

ARSENIC AND NON-MALIGNANT RESPIRATORY HEALTH OUTCOMES:  
EPIDEMIOLOGICAL EVIDENCE AND THE NEED FOR INTERVENTIONS IN  
AMERICAN INDIAN COMMUNITIES

by  
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## ABSTRACT

Inorganic arsenic, an established toxicant, has been associated with numerous health outcomes, including cancer of the lung. Evidence on the impact of arsenic exposure on nonmalignant respiratory outcomes, however, is less conclusive as studies examining low-moderate levels ( $<50\text{ }\mu\text{g/L}$ ) of water arsenic exposure are limited. In the US, elevated arsenic disproportionately affects populations relying on private well water, including many American Indian communities. Additionally, these communities have historically been at an increased risk of tuberculosis. This dissertation aimed to better understand the relationships between arsenic exposure and nonmalignant respiratory health outcomes in a population exposed to low-moderate arsenic from drinking water. We used data from the Strong Heart Study (SHS), a prospective cohort of American Indian adults, and the Strong Heart Water Study (SHWS), a randomized controlled trial aiming to reduce arsenic exposure in American Indian communities.

First, we conducted an analysis in 2,132 SHS participants to evaluate associations of arsenic exposure with lung health using urinary arsenic measurements at baseline (1989-1991) and spirometric measurements at Visit 2 (1993-1995). Arsenic exposure was positively associated with restrictive pattern, airflow obstruction, lower lung function, self-reported emphysema and having to stop for breath, independent of smoking and other lung disease risk factors.

Second, we evaluated the relationship between a history of active tuberculosis and subsequent lung function in 2,463 SHS participants. We observed that a history of active tuberculosis was associated with airflow obstruction, restrictive pattern, and respiratory symptoms. We found a reduced odds of tuberculosis with increasing arsenic exposure,

contrary to our hypothesis, but suggestive evidence of a possible synergistic interaction between arsenic and tuberculosis on worse lung function.

Third, we conducted a pilot study, in preparation for the SHWS, of 371 households to identify households with arsenic  $\geq 10$   $\mu\text{g/L}$ . Arsenic  $\geq 10$   $\mu\text{g/L}$  was found in 26.1% of households and median water arsenic concentration was 6.3  $\mu\text{g/L}$ , ranging from  $<1$  to 198  $\mu\text{g/L}$ . The study also tested and confirmed the effectiveness of a water filtration device to reduce water arsenic in these communities. The long-term efficacy of a community-based arsenic mitigation program in reducing arsenic exposure and preventing arsenic related disease is being tested as part of the SHWS.

In conclusion, low-moderate arsenic exposure may contribute to nonmalignant respiratory outcomes, including reduced lung function, respiratory symptoms, and a restrictive lung disease pattern. Our findings support existing knowledge that tuberculosis is a risk factor for long-term respiratory impairment. There is a relatively high burden of arsenic exposure in communities where the SHWS is being conducted, pointing to the continued need for effective interventions at the household level. More research is needed to investigate the association between arsenic exposure and non-malignant respiratory health, as many populations at risk of developing tuberculosis and other respiratory infections are also exposed to arsenic-contaminated water.

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## **PREFACE**

This dissertation is the final result of the research work conducted with my co-advisors, co-authors, and collaborators during my doctoral studies in the Department of Environmental Health and Engineering at the Johns Hopkins Bloomberg School of Public Health. This dissertation is organized in a manuscript format. First, we present our specific aims and then provide an overview of, and the motivations behind, this dissertation. We then review each of the analyses conducted, organized into three chapters. The first chapter evaluates the association between arsenic exposure with nonmalignant respiratory outcomes in the Strong Heart Study. The second chapter evaluates the association between a history of active tuberculosis and subsequent lung health, as well as the potential association between tuberculosis and arsenic exposure, in the Strong Heart Study. The third chapter evaluates the results of a water quality pilot study conducted for the Strong Heart Water Study. Finally, the discussion provides an overview of the research findings, strengths and limitations to the analyses, implications of the research, proposed next steps, and final conclusions.

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## ABBREVIATIONS

Body Mass Index (BMI)  
Chronic obstructive pulmonary disease (COPD)  
Confidence Interval (CI)  
Dimethylarsinic acid (DMA)  
Estimate Glomerular Filtration Rate (eGFR)  
Forced vital capacity (FVC)  
Forced expiratory volume in one second (FEV1)  
Inorganic Arsenic (iAs)  
Interquartile Range (IQR)  
Lower limit of normal, the 5th percentile of the frequency distribution of reference values (LLN)  
Maximum contaminant level (MCL)  
Monomethylarsonic acid (MMA)  
Odds ratio (OR)  
Randomized controlled trial (RCT)  
Strong Heart Study (SHS)  
Strong Heart Water Study (SHWS)

## **SPECIFIC AIMS**

Chronic respiratory diseases represent a major health burden around the globe, affecting hundreds of millions of people and resulting in four million premature deaths annually.<sup>1</sup> Chronic diseases of the airways represent a wide array of serious diseases, such as lung cancer, lung fibrosis, and chronic obstructive pulmonary disease, which includes bronchitis and emphysema.<sup>2</sup> In the United States (US), chronic obstructive pulmonary disease continues to be a leading cause of morbidity and mortality,<sup>3</sup> and restrictive disease is associated with a fair or poor self-reported health status.<sup>4</sup>

Respiratory disease is frequently avoidable, with prevention often costing a fraction of treatment.<sup>1</sup> Tobacco smoke, exposure to indoor and outdoor air pollutants, allergens, and occupational exposures are important modifiable risk factors of chronic respiratory diseases,<sup>5</sup> but there is need for research to identify relevant environmental factors that are less well established, especially as chronic respiratory disease is increasing in prevalence.<sup>1, 2</sup>

The role of arsenic, an established toxicant and carcinogen, through ingestion from drinking water on lung cancer risk is well established, with the International Agency for Research on Cancer classifying arsenic in drinking water as a type 1 lung carcinogen.<sup>6, 7</sup> However, evidence on the impact of arsenic exposure on nonmalignant outcomes, such as lung function and exacerbation of respiratory symptoms, is less conclusive. Existing evidence supports an association between arsenic exposure with lung function, respiratory symptoms, lower respiratory infections, bronchiectasis, and tuberculosis;<sup>8-10</sup> however, most studies are in populations exposed to higher arsenic levels in drinking water ( $>50 \mu\text{g/L}$ ).<sup>11-26</sup> A recent systematic review showed strong evidence of

a general association between arsenic and nonmalignant respiratory diseases at high levels of arsenic exposure,<sup>24</sup> but the evidence base is in need of additional prospective studies, especially at low-moderate levels (<50 µg/L) of arsenic exposure. Further, few studies conducted in the US have investigated the association between arsenic and respiratory health.<sup>15, 16, 27</sup>

Elevated exposure to arsenic disproportionately affects populations relying on private well water in the US. Rural and suburban families relying on ground water, including many in American Indian communities, are the most affected, especially in portions of the Southwest, Midwest and Northeast US.<sup>28</sup> Private wells do not fall under the jurisdiction of the US Environmental Protection Agency's Safe Drinking Water Act, and it is the responsibility of the well owner to make sure their water is safe. Major barriers to arsenic water testing exist, including general awareness and lack of access to water testing.<sup>29</sup> In American Indians who participated in the Strong Heart Study, a population-based study ongoing since 1988 comprised of tribal members from Oklahoma, Arizona, North Dakota, and South Dakota, elevated exposure arsenic from private well water has been associated with numerous health outcomes<sup>30-33</sup> including increased mortality for lung cancer.<sup>33</sup> Additionally, these same communities historically have been at an increased risk of tuberculosis due to a higher than average prevalence of predisposing risk factors, such as diabetes, smoking, and socioeconomic circumstances.<sup>34</sup> Little is known about the nonmalignant respiratory health outcomes in this population, either associated with a past history of tuberculosis, which is commonly associated with long-term pulmonary damage,<sup>35</sup> or chronic arsenic exposure, both of which could potentially be contributing to an unmeasured burden of chronic lung disease.

Additionally, minority groups, including American Indians, are underrepresented in published biomedical and clinical research on pulmonary disease,<sup>36</sup> further pointing to the need to investigate the group's respiratory health.

The main objectives of this dissertation were to (1) evaluate the relationship between arsenic exposure and nonmalignant respiratory health in a population chronically exposed to low-moderate arsenic levels; (2) evaluate the impact of tuberculosis survival on lung function and its potential association with arsenic exposure in the Strong Heart Study; and (3) conduct water arsenic testing and a water quality assessment pilot for the Strong Heart Water Study intervention, aimed at reducing water arsenic at the household level to improve health outcomes.

The **hypotheses** of this dissertation were:

- 1) In the Strong Heart Study population, a US population chronically exposed to low-moderate arsenic levels through drinking water, lung function is reduced and respiratory symptoms are increased, independent of smoking status and dependent on arsenic levels.
- 2) In the Strong Heart Study population, a history of active tuberculosis and subsequent recovery is associated with consequent reduced lung function and increased respiratory symptoms. Elevated arsenic levels are associated with an increased odds of a past history of active tuberculosis. Elevated arsenic levels and history of active tuberculosis synergistically interact on reduced lung function and increased respiratory symptoms.
- 3) In the Strong Heart Water Study setting of low-moderate arsenic levels, arsenic above the maximum contaminant level of  $\geq 10$   $\mu\text{g/L}$  in drinking water is common, and a selected



point-of-use adsorptive media filter, for use in the intervention, will be effective at reducing arsenic levels and providing arsenic safe water for drinking and cooking.

To test these hypotheses, we used data from the Strong Heart Study (SHS), a population-based prospective cohort study designed to investigate cardiovascular disease, diabetes and their risk factors in American Indians, as well as the Strong Heart Water Study (SHWS), a randomized controlled trial intervention that delivers a water arsenic removal device at the household level, designed to include SHS members. The SHS and SHWS serve as ideal populations to understand the relationship between low-moderate arsenic exposure and respiratory outcomes given widespread exposure to arsenic through drinking water and the availability of multiple measures of respiratory health status.

The **specific aims** were the following:

Aim 1: To evaluate the association of arsenic exposure with lung function and respiratory health using collected SHS data. To complete this aim, we conducted an analysis using urinary arsenic measurements at baseline (1989-1991) and spirometry measures, self-reported respiratory symptoms, and self-reported respiratory nonmalignant disease at Visit 2 (1993-1995) from 2,132 participants.

Aim 2: To evaluate the impact of active tuberculosis survival on lung health in an historically highly impacted population of American Indians. We conducted an analysis using tuberculosis data and spirometry measures from the Visit 2 examination (1993 – 1995) in 2,463 individuals. In an additional analysis, we evaluated the potential

association between a history of active tuberculosis and arsenic exposure and their possible interaction on lung disease.

Aim 3: To identify households with private wells with elevated arsenic that are eligible for the SHWS, using inductive coupled plasma mass spectrometry vs. a rapid arsenic screening tool, and to assess the efficacy of a selected point-of-use adsorptive media filter and water quality parameters that could interfere with the efficacy of the filter. To complete this aim, we conducted a pilot study where 371 households were tested for arsenic  $\geq 10$   $\mu\text{g/L}$  between 2014 – 2018. A more detailed water quality assessment was performed in 29 of these households.

Nonmalignant respiratory disease can have a profound negative effect on quality of life.<sup>37</sup> Efforts to understand environmental risk factors are critical, as is understanding the implications of arsenic at low-moderate exposure levels on respiratory health, particularly as it is an understudied health effect. With SHS participants continually affected by exposure to arsenic, especially those on private well water, the need for an effective intervention at the household level is necessary. This dissertation provides a thorough investigation into the association between arsenic exposure and nonmalignant respiratory health, presenting evidence to support future arsenic health effects prevention trials and in the context of identifying high risk groups for the development of respiratory disease.

## **INTRODUCTION**

### **Overview**

In this chapter we review the existing literature on the following topics: (1) lung health in American Indian communities; (2) epidemiological evidence on arsenic induced patterns of respiratory disease; (3) experimental evidence on arsenic exposure with respiratory disease; (4) factors affecting lung health; and (5) diabetes as a sensitivity analysis.

### **Lung Health in American Indian Communities**

In comparison to the general US population, American Indians and Alaska Natives, comprised of an estimated 2.3 million individuals who identified themselves in 2008 solely as such,<sup>1</sup> have increased rates of infectious lung diseases and lower rates of smoking-related diseases.<sup>2</sup> At the time the Strong Heart Study Phase II was taking place (1993-1995), the most prominent respiratory diseases in American Indian adults were pneumonia, lung cancer, chronic obstructive pulmonary disease, and tuberculosis.<sup>3</sup> Historically, a low prevalence of asthma has been reported in the American Indian population,<sup>3</sup> but in the SHS, underdiagnosis of asthma has been a concern, as 4% of participants in the SHS's third examination (1998-1999) had probable but previously undiagnosed asthma.<sup>4</sup> Limited information is available on the occurrence of chronic obstructive pulmonary disease (COPD) among American Indians, but the mortality rate was approximately one-third compared to the rate for all races in the US (years 1984 – 1988), although mortality studies based on death certificate data are well known to

severely underestimate the burden of disease in American Indian communities. Mortality rates for COPD were lower among American Indians in the Southwest, where smoking rates are lower, as compared to rates for American Indians of the Great Plains, where smoking is common.<sup>2</sup> Similarly, lung cancer mortality rates for American Indians are much higher in north central states as compared to the southwest due to much higher smoking rates. However, even in the north central states, where the rates of smoking exceed those of the rest of the population, the rates of deaths from lung cancer are only just slightly more than one-half the rate for all races in the US. Tuberculosis, even as incidence among American Indians has declined, remains disproportionately high when compared to incidence among the white population.<sup>2</sup> Possible reasons for increased mortality from tuberculosis include diabetes incidence, poverty and socioeconomic conditions, smoking, and alcohol use.<sup>2</sup> Individuals with diabetes from the Oglala Sioux Tribe were 5.2 times more likely to progress to active tuberculosis disease than non-diabetic individuals with a positive tuberculin test.<sup>5</sup> Additionally, Indian Health Service facilities often have been understaffed, particularly in North/South Dakota, resulting in tuberculosis preventative measures being postponed to deal with more urgent emergencies.<sup>5</sup>

### **Epidemiological Evidence on Arsenic Induced Patterns of Respiratory Disease**

Spirometry is a frequently used method for assessing lung function.<sup>6</sup> The main parameters used to assess lung function include: the forced expiratory volume in one second (FEV1), the forced vital capacity (FVC), and forced expiratory ratio

(FEV1/FVC). While spirometry does not diagnose lung disease, different patterns of spirometry can identify specific abnormalities associated with certain lung diseases and can be classified as obstructive or restrictive. Obstructive diseases, like chronic obstructive pulmonary disease, an umbrella term used to describe progressive lung diseases including emphysema and chronic bronchitis, are characterized by persistent airflow limitations, breathlessness, and a reduced FEV1/FVC and FEV1 with a preserved FVC.<sup>7</sup> Major risk factors include smoking, occupational exposures, and air pollution. Asthma is another obstructive lung disease that can have reversible, intermittent, or permanent changes in spirometric lung function measurements. Restrictive pulmonary abnormalities, characterized by a reduced FEV1 and FVC with a stable or higher FEV1/FVC, result in a decreased total lung capacity as a result of reduced lung compliance.<sup>7, 8</sup> Restrictive lung impairment can be intrinsic, resulting from inflammation or scarring of lung tissue as a result of disease like pulmonary fibrosis, or extrinsic, resulting from disorders affecting respiratory muscle function, such as scoliosis and muscular dystrophy.<sup>8</sup> Major risk factors include diabetes, waist circumference, smoking, and occupational exposures. An obstructive pattern of lung impairment is found in approximately 13.6% of US adults, and restrictive impairment is found in 6.5%, with only minimal changes found when comparing rates from 1988-1994 and 2007-2010, indicating an enduring disease burden.<sup>9</sup> In addition, lung diseases have been found to be associated with repeat hospitalizations, higher health care costs, and poor quality of life.<sup>9-</sup>

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FEV1 and FVC. Across the body of evidence from general populations exposed to arsenic in drinking water, increasing arsenic exposure was associated with a decline in

lung function.<sup>12</sup> Several studies from arsenic-endemic areas in South Asia reported lower FEV1 and FVC among study participants with very high levels of arsenic in drinking water ( $>250 \mu\text{g/L}$ ).<sup>13, 14</sup> A study from India investigating the impact of low-moderate arsenic exposure on lung function found that those exposed to  $11\text{-}50 \mu\text{g/L}$  compared to  $<10 \mu\text{g/L}$  had 500 mL lower mean FVC ( $p < 0.001$ ), as well as lower FEV1.<sup>15</sup> In a meta-analysis of nine studies with water arsenic levels ranging from 23 to  $860 \mu\text{g/L}$ , arsenic exposure was associated with lower FEV1 and FVC.<sup>16</sup> In a recent study from the US, no association was seen with arsenic exposure and lung function.<sup>17</sup>

FEV1/FVC ratio. In a recent meta-analysis which excluded studies where arsenic skin lesions were the only exposure marker,<sup>16</sup> only three studies reported effects estimates for the FEV1/FVC ratio,<sup>13, 18, 19</sup> for which the meta-analysis found no evidence of an association, suggestive of restrictive lung deficits. A large population study in Bangladesh found inverse but not statistically significant associations between arsenic exposures measured in urine or water with FEV1/FVC, however the data were not shown.<sup>20</sup> In a recent study examining NHANES data with individual spirometry measurements and urinary arsenic, no significant association was found in relation to FEV1/FVC ratio.<sup>17</sup>

Strong Heart Study spirometry reference values. At the time of the SHS Visit 2 (1993-1995), reference equations derived from a sample of the general US population from the National Health and Nutrition Examination Study (NHANES) III did not include American Indians.<sup>21</sup> Marion et. al used data from the Strong Heart Study to derive normative values for the SHS. In order to have reliable reference values used for the prediction of lung function, the reference cohort should be representative and free of

factors interfering with the results;<sup>22</sup> the reference group used to derive SHS normative values excluded individuals with variables that were significant predictors of FEV1, including cigarette smoking >10 pack-years, asthma or wheezing, diabetes, or indexes of obesity.

Respiratory symptoms. A systematic review examined eighteen publications investigating the relationship between arsenic and respiratory symptoms.<sup>12</sup> The studies reported anywhere from one to nineteen different symptom-related endpoints, either individually or combined. Results have been mixed, with some studies finding statistically significant positive associations between arsenic and at least one respiratory symptom,<sup>15, 23-30</sup> while others found no significant association between arsenic levels and any respiratory symptom assessed.<sup>13, 14, 18, 31-33</sup>

Respiratory disease. Only a small number of studies have examined chronic bronchitis, emphysema, and asthma with arsenic exposure; as a result, the relationship between arsenic and specific chronic nonmalignant lung disease is not clear.<sup>12</sup> A study from the US reported a greater odds of self-reported emphysema among those with the highest quartile of arsenic exposure (>17.23 µg/L) compared to those in the lowest quartile (<3.52 µg/L), but results were not statistically significant (OR=1.29, 95% CI=0.17, 9.82).<sup>33</sup> The study also reported those in the highest quartile of exposure had lower odds of self-reported chronic bronchitis compared to those in the lowest quartile, but results did not achieve statistical significance after adjustments (OR=0.77, 95% CI=0.24, 2.51). The direction of this finding is inconsistent with three other studies on chronic bronchitis, two of which found increased odds of chronic bronchitis in those with arsenical skin lesions.<sup>14, 31, 34</sup> For asthma, no increase in mortality was identified in an

arsenic-exposed region in Taiwan,<sup>35</sup> and in the US population, a reduced odds of asthma was found, but the results were not statistically significant (OR=0.71, 95% CI=0.41, 1.24).<sup>33</sup>

### **Experimental Evidence on Arsenic Exposure with Respiratory Disease**

Despite epidemiologic evidence, little is known regarding arsenic-induced effects on airway physiology;<sup>36, 37</sup> although a number of studies have shown that arsenic is deposited in the lung, particularly in the epithelium.<sup>38</sup> Results of epidemiological studies have suggested that arsenic exposure is linked to chronic loss of lung defenses, including the secretion of clara cell secretory protein (CC16), a protein that plays major role in protecting alveolar epithelium from pollutants, from airway cells.<sup>24, 38</sup>

In mice, exposure of low to moderate concentrations of arsenic in drinking water (10 – 100 ppb) led to a decrease in immune gene expression and aberration in inflammatory protein expression.<sup>39, 40</sup> As a result, mice were more susceptible to airway inflammation.<sup>41</sup> Other mice studies suggest genes which sustain wound repair, lung matrix, and barrier function are comprised with arsenic exposure.<sup>42-44</sup> Increased expression of matrix metalloproteinase-9 (MMP-9), a matrix degradation enzyme, might be an important biomarker of the inhibitory effect of arsenic on lung function.<sup>45, 46</sup> In confluent human airway epithelial cells, arsenic increased time to close a scratch wound; this reduced wound repair was associated with increased expression of MMP-9 activity.<sup>47</sup> Airway remodeling is a hallmark of a number of respiratory diseases; changes in



expression and organization of extracellular matrix genes and in expression of mediators and enzymes that control matrix remodeling have consistently been observed.<sup>47</sup>

### **Factors Impacting Lung Health**

Reference values for spirometry are based on the most important anthropometric factors of height, age, sex, and race. Historically, age has been a major factor when examining the lung, as lung function begins to decline after reaching pulmonary maturity at about 20-25 years of age.<sup>48</sup> The lung is affected by advancing age by impairment in respiratory mechanics, including rigidity of the chest wall, decreased diameter of small airways, and decreased elastic recoil of the lung.<sup>49</sup> There is debate over whether the diagnostic thresholds that define spirometric obstruction are adequate for age-related changes. The Global Initiative for Obstructive Lung Disease (GOLD) threshold of  $<0.70$  for FEV1/FVC is thought to often misclassify normal spirometry as airflow obstruction in non-smokers, particularly in older adults.<sup>50</sup> The American Thoracic Society recommends using the lower limit of normal (LLN) instead of the fixed GOLD ratio. The LLN is statistically defined by the lower 5<sup>th</sup> percentile of a reference population, calculated by subtracting 1.64 times the standard deviation from the mean (expected value).<sup>51</sup> However, it is likely that the LLN misses individuals with mild airflow obstruction,<sup>51</sup> and underdiagnosis of obstruction may be a larger problem than overdiagnosis.<sup>52</sup>

Height also affects lung function measurements. Taller individuals have greater lung capacity, so their lung volume will decrease at a greater rate compared to shorter individuals as they age. Among individuals of the same weight and height, men have

larger lungs than women, resulting in a larger number on bronchi and greater alveolar surface area. Men tend to have higher airflow values than women, but FEV1 decreases with age more rapidly in men than in women due to respiratory muscle strength decreasing more significantly in men.<sup>48</sup>

There are many factors that are relevant to lung health in certain cases that are not taken into account by reference standards, including lifestyle factors and environmental exposures. Tobacco smoking in adults is a well-established risk factor for lung disease, including acceleration of age-related decline in lung function and increased respiratory symptoms.<sup>53</sup> Body mass index can affect pulmonary physiology, influencing breathing pattern and respiratory mechanics.<sup>54</sup> Indoor air pollution related to biomass fuel, such as heating with an open fireplace in developed countries, has been associated with lung disease including COPD, risk of developing pulmonary tuberculosis, and faster decline in lung function.<sup>55</sup> Outdoor air pollutants like particulate matter have been shown to affect chronic lung health, with a possible significant association between particulate matter concentrations and the rate of age-related decline in FEV1.<sup>56</sup>

### **Diabetes as a Sensitivity Analysis**

In Chapter 1, when examining the association between lung health and arsenic, we conducted sensitivity analyses by further adjusting models for diabetes. Diabetes was treated as a sensitivity analysis; the temporal and causal relationship between diabetes and lung function is debated. Cross-sectional studies have found that individuals with diabetes often have reduced lung function compared to those without diabetes,<sup>57-59</sup> but the

definitive direction in addition to the pathophysiological mechanism to explain the association between lung function and diabetes is not known.<sup>60</sup> A cross-sectional study of older individuals without a history of chronic lung disease found duration of diabetes to be associated with reduced lung function, suggesting diabetes duration influences lung function more than glycemic control, and that obesity may also contribute.<sup>61</sup> In a large longitudinal study (N= 27,711), a low FEV1 preceded and significantly predicted future diabetes, with the relationship not fully explained by inflammation, smoking, or obesity.<sup>62</sup> There is likely a complex model of diabetes-related lung damage;<sup>61</sup> proposed mechanisms for the relationship between reduced lung function and diabetes include chronic inflammation, microangiopathy of lung vasculature, and loss of elastic recoil due to glycosylation of lung parenchyma.<sup>62</sup> With consideration to the body of research examining arsenic exposure and lung function, previous studies have not adjusted for diabetes.<sup>12</sup> The SHS population has a high rate of diabetes, with prevalence close to 50%,<sup>63</sup> and impaired lung function has been found to present before the development of diabetes.<sup>64</sup> Additionally, there is a large body of evidence suggesting that chronic arsenic exposure can contribute to diabetes development, further pointing to the need for a sensitivity analysis in our evaluation of the relationship between arsenic and lung health in the SHS.<sup>65</sup>

## CHAPTER 1

### Low-moderate arsenic exposure and respiratory health in American Indian communities in the Strong Heart Study

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## ABSTRACT

**Background:** Arsenic exposure through drinking water is an established lung carcinogen. Evidence on non-malignant lung outcomes is less conclusive and suggests arsenic is associated with lower lung function. Studies examining low-moderate arsenic exposure ( $<50\text{ }\mu\text{g/L}$ ), the level relevant for most populations, are limited. We evaluated the association of arsenic exposure with respiratory health in American Indians from the Northern Plains, the Southern Plains and the Southwest United States, communities with environmental exposure to inorganic arsenic through drinking water.

**Methods:** The Strong Heart Study is a prospective study of American Indian adults. This analysis used urinary arsenic measurements at baseline (1989-1991) and spirometry at Visit 2 (1993-1995) from 2,132 participants to evaluate associations of arsenic exposure with airflow obstruction, restrictive pattern, self-reported respiratory disease, and symptoms.

**Results:** Airflow obstruction was present in 21.5% and restrictive pattern was present in 14.4%. The odds ratio (95% confidence interval) for obstruction and restrictive patterns, based on the fixed ratio definition, comparing the 75th to 25th percentile of arsenic, was 1.17 (0.99, 1.38) and 1.27 (1.01, 1.60), respectively, after adjustments, and 1.28 (1.02, 1.60) and 1.33 (0.90, 1.50), respectively, based on the lower limit of normal definition. Arsenic was associated with lower percent predicted FEV1 and FVC, self-reported emphysema and stopping for breath.

**Conclusions:** Low-moderate arsenic exposure was positively associated with restrictive pattern, airflow obstruction, lower lung function, self-reported emphysema and stopping

for breath, independent of smoking and other lung disease risk factors. Findings suggest that low-moderate arsenic exposure may contribute to restrictive lung disease.

## INTRODUCTION

Arsenic exposure via drinking water is a well-established lung carcinogen <sup>1-3</sup>. More recently, water arsenic >100 µg/L has been associated with non-malignant respiratory effects, including respiratory symptoms and worse lung function tests. A recent meta-analysis identified an association between arsenic exposure and reduced forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) with a preserved ratio (in subset of 3 studies reporting FEV1/FVC), indicating a possible association with restrictive lung disease <sup>4</sup>. The studies in the meta-analysis included a wide range of exposure levels, with arsenic often ten times higher than the World Health Organization guideline/United States Environmental Protection Agency standard of 10 µg/L in drinking water. More evidence is needed regarding the risks associated with low-moderate levels of arsenic exposure (<50 µg/L), and levels common in the US and other countries (<10 µg/L). A recent systematic review showed strong evidence of an association between high levels of arsenic exposure with respiratory symptoms, non-malignant respiratory illness, and reduced lung function <sup>5</sup>. One study from the US found no association between low-moderate arsenic exposure and self-reported diagnosis or symptoms of obstructive lung disease but lacked spirometry data <sup>6</sup>. We examined the association of low-moderate arsenic exposure with respiratory health in American Indians from the Northern Plains, the Southern Plains and the Southwest United States, communities with environmental exposure to inorganic arsenic through drinking water.

## METHODS

### Study population

The Strong Heart Study (SHS) is an ongoing population-based, prospective study of cardiovascular disease and its risk factors in American Indian adults. The SHS recruited 4,549 residents of Tribal Nations from study sites located in Arizona (AZ), Oklahoma (OK), and North Dakota and South Dakota (ND/SD) in the US. Study enrollment rates were 71.8% in AZ, 61.5% in OK, and 55.3% in ND/SD <sup>7</sup>. All men and women aged 45 to 74 years at the baseline visit in 1989-1991 were invited to participate, with subsequent clinical visits <sup>8</sup>. In 2016, one community in Arizona withdrew their consent, reducing the cohort to 3,516 participants. To account for the unintended withdrawal of a Tribal Nation, all analyses were weighted using inverse probability weighting. As study site proportion is known from the original cohort, the withdrawal of the Tribal Nation was adjusted for by weighting the remaining participants, with approximately 1/3 of weight for each center (33.0% AZ, 33.6% OK, 33.4% ND/SD); the use of the statistical weight is to reduce bias introduced by drop-out <sup>9</sup>.

This study used urinary arsenic data from the baseline examination and spirometry from Visit 2 (1993-1995), both available in 2,271 participants. We excluded 94 participants missing baseline data on smoking status and cigarette pack-years, 11 missing diabetes status, education, or body mass index (BMI), and 34 missing tuberculosis data, leaving 2,132 participants for our analyses.

### **Data collection**

Visits included biospecimen collection, physical exam, and an interviewer-administered standardized questionnaire. Visits were performed by trained and certified examiners. Details have been described previously <sup>8</sup>.



## **Urine arsenic**

Morning spot urine samples were collected at baseline <sup>8</sup>. For arsenic analyses, urine concentrations of inorganic arsenic (iAs), methylarsonate (MMA), and dimethylarsinate (DMA) were measured using high performance liquid chromatography/inductively coupled plasma-mass spectrometry. The metabolism of inorganic arsenic in the human body results in MMA and DMA which are excreted in urine together with unchanged inorganic arsenic. Quality control and assurance methods and laboratory procedures for urine analysis have been previously described <sup>10</sup>. We used the sum of inorganic and methylated arsenic species (iAs+MMA+DMA) as the biomarker of exposure to inorganic arsenic in drinking water and food. Arsenobetaine levels are low in the population (median (10<sup>th</sup>, 90<sup>th</sup> percentiles): 0.5 µg/g (<0.6 – 6.10 creatinine)], confirming that seafood intake is rare <sup>11</sup>. Urine arsenic concentrations (µg/L) were divided by urine creatinine concentrations (g/L) to account for urine dilution in spot urine samples and expressed as concentrations of total urine arsenic and its species in µg/g creatinine.

## **Spirometry for Identification of Airflow Obstruction and Restrictive Pattern**

Spirometry was performed by trained and certified nurses and technicians <sup>12</sup>. Pre-bronchodilator testing was conducted while sitting, except for participants with BMI >27 kg/m<sup>2</sup> who stood. Maneuvers were considered acceptable to then-current 1994 American Thoracic Society recommendations <sup>12, 13</sup>.

Spirometric measurements FEV1, FVC, and FEV1/FVC were used in analyses. Reference values for SHS participants were derived previously<sup>12</sup> yielding FVC %predicted and FEV1 %predicted. The prevalence of airflow obstruction was defined by a fixed ratio of FEV1/FVC<0.70 using crude values<sup>14</sup>. A low FVC (<80 %predicted) together with a preserved ratio (FEV1/FVC≥0.70) was defined as restrictive pattern<sup>15</sup>. Healthy individuals (controls) were those with no-obstruction and no-restriction (FEV1/FVC>0.70 and FVC>80 %predicted). We conducted secondary analyses with the lower limit of normal (LLN = 5<sup>th</sup> percentile of the frequency distribution of reference values; obstruction: FEV1/FVC <LLN; restriction: FEV1/FVC >LLN and FVC <LLN; healthy: FEV1/FVC >LLN and FVC >LLN).

### **Symptoms and Lung Disease**

At Visit 2, participants were asked to report respiratory symptoms including cough (“Do you usually have a cough?”, frequent cough (“Do you usually cough as much as 4-6 times/day, 4 or more days/week?”), cough with phlegm (“Do you usually bring up phlegm when you cough?”), shortness of breath (“Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?”), and stopping for breath while walking (“Do you ever have to stop for breath while walking about 100 yards or a few minutes on the level?”). Participants self-reported emphysema, asthma, or chronic bronchitis diagnoses, which was recorded at Visit 2.

### **Other variables**

At the baseline visit, sociodemographic (age, sex, education, and study site) and life-style (smoking status and smoking pack-years) variables were ascertained through a standardized questionnaire by trained and certified interviewers <sup>8</sup>. Smoking status was categorized as never, former, or current. Former: smoked  $\geq 100$  cigarettes but no longer smoking; Never: smoked  $< 100$  cigarettes in lifetime; and Current: smoking at then-present day. Height and weight measurements for BMI calculation (weight in kilograms divided by height in meters squared) were conducted during the physical exam. Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR)  $< 60$  ml/min/1.73m<sup>2</sup> based on serum creatinine using the Modification of Diet in Renal Disease equation <sup>16</sup>. Diabetes was defined as a fasting glucose level of  $\geq 126$  mg/dL, a 2-hour post-load plasma glucose level of  $\geq 200$  mg/dL, an HbA1c level of  $\geq 6.5\%$ , or use of an oral hypoglycemic agent or insulin <sup>17</sup>.

At Visit 2, a medical record review for a history of active and treated tuberculosis (class III tuberculosis) was performed. Case definition for class III tuberculosis involved having a positive culture for *Mycobacterium tuberculosis* from a body fluid or tissue or having a clinical picture suggestive of tuberculosis that responded to treatment with antitubercular medications. If the individual had active tuberculosis listed on a discharge diagnosis or on a problem list, they were considered to have a history of tuberculosis.

### **Statistical analysis**

We conducted descriptive statistics to evaluate differences in participant demographic and lifestyle variables by obstruction and restrictive pattern and by urinary arsenic tertile. We used logistic regression to estimate the odds ratio [OR] for presence of

obstruction/restrictive pattern, respiratory symptoms and disease by urinary arsenic concentrations, and linear regression to assess the mean difference of spirometric measurements. We modelled arsenic exposure using three approaches: a categorical variable, comparing tertiles of arsenic exposure; a continuous variable to compare an interquartile (IQR) increase of log urinary arsenic; and a continuous variable with splines with knots at the 10<sup>th</sup>, 50<sup>th</sup>, and 90<sup>th</sup> percentiles (3.8, 10.2, and 25.8 µg/g creatinine, respectively) to allow for a flexible dose-response relationship. *P* values for trend were obtained from modelling log-arsenic as continuous. Models were progressively adjusted (see footnotes of Tables 3, 4, 6).

Effect modification of the association was evaluated depending on confounding variables by including interaction terms for log-transformed urinary arsenic concentrations with indicator variables for sex, age, smoking status, BMI, and diabetes. *P* values for interactions were obtained using Wald test for multiple coefficients. To evaluate arsenic metabolism, we examined the association between the relative proportions of arsenic species in urine per 5% change and presence of obstruction/restrictive pattern.

## RESULTS

Obstruction was present in 21.5% (458/2,132) and restrictive pattern present in 14.4% (307/2,132). Obstruction and restrictive pattern demographics are described in Table 1. Obstruction was present in 31.0% vs. 20.7% of participants in the highest vs. lowest arsenic exposure tertiles (*p*=0.02); restrictive pattern was present in 23.8% vs. 17.2% of participants in corresponding tertiles (*p*<0.001) (Table 2).

After full adjustment (Table 3, model 3), the odds ratio [95% CI] comparing the highest to lowest arsenic tertile ( $\geq 14.0$  vs.  $\leq 7.0$   $\mu\text{g/g}$  creatinine) was 1.33 [0.99, 1.77] for obstruction and 1.34 [0.92, 1.96] for restrictive pattern. The corresponding OR [95%CI] comparing an interquartile range (IQR) of arsenic was 1.17 [0.99, 1.38] ( $P$  for trend 0.07) for obstruction and 1.27 [1.01, 1.60] ( $P$  for trend 0.04) for restrictive pattern (Table 3, model 3). Modelling urinary arsenic using flexible splines, there was some departure from linearity (Figure 1). Results were unchanged in analyses excluding 5 participants above the 99<sup>th</sup> percentile of %predicted FEV1 and FVC (results not shown). In a sensitivity analysis with further adjustment for diabetes, the OR for obstruction per change in arsenic IQR remained similar (1.17 [0.99, 1.40] ( $P$  for trend 0.07)), and for restrictive pattern the OR was attenuated (1.18 [0.93, 1.50] ( $P$  for trend 0.18)) (Table 3).

Using the LLN definition, obstruction was present in 7.1% (151/2,132) and restrictive pattern in 6.9% (147/2,132). The ORs for the association based on the LLN were stronger compared to the fixed ratio and were significant for obstruction (OR [95%CI] per IQR) (1.28 [1.02, 1.60] ( $P$  for trend 0.03) but non-significant for restriction (1.33 [0.90, 1.50] ( $P$  for trend 0.06) (Table 4).

The mean difference [95% CI] for FEV1 %predicted for an IQR change in urinary arsenic was -1.39 [-2.51, -0.25] ( $P$  for trend 0.02), although the trend was non-linear by tertile (Table 5) and flexible splines (Figure 2). The %predicted association remained significant after further adjustment for diabetes in the sensitivity analyses (Table 1S). For FVC %predicted, the mean difference [95% CI] per IQR change in arsenic was -1.13 [-2.21, -0.05] ( $P$  for trend 0.04). Among the healthy group, the mean difference for FEV1

%predicted and FVC %predicted both became non-significant (Table 5) and remained non-significant in the sensitivity analysis (Table 1S). No association was found between arsenic and FEV1/FVC. Using crude FEV1 and FVC measures (mL) the mean differences were significant (Table 5).

We found no effect modification for the association of arsenic with obstruction/restrictive pattern by age, BMI, or diabetes (Table 2S). By sex, effect modification was significant for obstruction ( $P=0.003$ ), with an association found in men (OR [95%CI]) (1.47 [1.07, 2.06]) but not significant in women (1.07 [0.82, 1.33]). By smoking status, the association with arsenic was strongest in former smokers both for obstruction (1.74 [1.20, 2.55]) and restrictive pattern (1.34 [0.82, 2.17]) compared to never or current smokers, but confidence intervals overlapped in both analyses. Urinary relative proportions of iAs, MMA, and DMA were not associated with obstruction/restrictive pattern (Table 4S).

Urinary arsenic was inversely associated with cough (OR [95%CI] per IQR) (0.78 [0.65, 0.93]), but not with frequent cough (4-6x/day) or production of phlegm (Table 6). There was no association between arsenic and shortness of breath, but arsenic was positively associated with stopping for breath while walking (1.41 [1.19, 1.69]) (Table 6). Urinary arsenic was positively associated with emphysema (OR [95%CI] per IQR) (1.66 [1.29, 2.15]); inversely associated with asthma (0.76 [0.61, 0.96]) and not associated with chronic bronchitis (Table 3S).

## DISCUSSION

Exposure to low-moderate levels of inorganic arsenic was associated with increased odds of fixed ratio restrictive lung pattern, lower FEV1 and lower FVC, borderline associated with fixed ratio obstruction, and not associated with FEV1/FVC. The associations based on the LLN became stronger and significant for obstruction and stronger but non-significant for restrictive pattern. Arsenic was also associated with stopping for breath while walking and with higher self-reported emphysema. The association with restrictive pattern is consistent with recent meta-analysis findings that suggested low-level arsenic exposure is a restrictive lung disease risk factor <sup>4</sup>. There is debate over using the fixed ratio definition of obstruction, which can potentially lead to over-diagnoses in older patients <sup>18,19</sup>. However, there are also limitations with LLN-defined obstruction, which can underestimate COPD <sup>20</sup>. The stronger but non-significant effect estimates we observed for the association between arsenic and LLN-defined restrictive pattern may be due to a more specific definition and exclusion of less severe cases.

Restrictive pattern findings remained significant after adjustment for smoking (status and pack-years), a major risk factor for reduced pulmonary function <sup>21,22</sup>. In a sensitivity analysis (results not shown), we adjusted for additional adiposity factors (% body fat, waist circumference) to account for mechanical constraints of obesity-related lung restriction <sup>23</sup> with consistent findings. Adjustment for diabetes, however, attenuated the association, which became non-significant. The definitive direction as well as the exact pathophysiological mechanism to explain the association between diabetes and lung function is not known <sup>24</sup>; in the Strong Heart Study, impaired lung function presented

before the development of diabetes <sup>25</sup>. Previous similar studies have not adjusted for diabetes, but a large body of evidence suggests that chronic arsenic exposure can contribute to diabetes development <sup>26</sup>, and diabetes could be in the causal pathway between arsenic and restrictive lung pattern.

There is consistent evidence that increasing arsenic exposure is associated with reports of coughing and breathing problems <sup>5</sup>. However, we only found a positive association between arsenic and the need to stop for breath and a reduced odds of cough. One study in the US also found lower odds of chronic cough in participants with greater than the 80<sup>th</sup> arsenic percentile (<17.23 µg/L) compared to those with less than the 20<sup>th</sup> percentile (<3.52 µg/L) <sup>6</sup>. The same study reported greater odds of self-reported emphysema, similar to our findings, among those with the highest quartile of urinary arsenic compared to the lowest, but results were non-significant <sup>6</sup>. Four studies have examined arsenic and chronic bronchitis; three found a greater odds <sup>27-29</sup> and one found reduced odds.<sup>6</sup>

Despite epidemiologic evidence, little is known regarding arsenic-induced effects on airway physiology <sup>30,31</sup>. Rather than a direct toxic effect of arsenic on the lung, an inflammation-mediated immunologic basis has been suggested <sup>32</sup>, as arsenic is known to alter key functions of the innate and adaptive immune system <sup>33-36</sup>. One possible mechanism is aberrant airway remodeling targeted by arsenic following activation of inflammatory mediators. Airway remodeling has been linked to the equilibrium between proteases matrix metalloproteinase-9 (MMP-9) and its inhibitors, receptor for advanced glycation end products (RAGE) <sup>37</sup>. Loss of the soluble form of RAGE, sRAGE, is related to functional changes of pulmonary cell types, with consequences of fibrotic disease.



Arsenic may change RAGE gene expression by altering the promoter region methylation or by affecting transcriptional regulators of RAGE. In humans, sputum sRAGE levels were negatively correlated with urinary arsenic levels, similar to animal models <sup>38</sup>. In vitro models have shown arsenic exposure increased activity and expression of MMP-9 in airway epithelial cells <sup>39</sup>.

This study had several limitations. We measured urinary arsenic levels in a single sample at baseline, while spirometric measurements were taken at Visit 2. However, the temporal stability of arsenic levels in drinking water and urine has been shown in this population <sup>11</sup>. Spirometry was originally performed for better prediction of cardiovascular disease <sup>13</sup>. We did not have total lung capacity measurements, often not available for large population screenings, and could not confirm restriction presence by methods other than spirometry. Thus, we cannot discard the possibility that the association we found may be due to mixed ventilatory defect. Outcome misclassification could have occurred from inaccurate recall of disease diagnosis. The reason we saw a significant relationship between arsenic and obstruction only in former smokers is unknown. A few studies have reported similar findings, with authors suggesting the toxic effects of smoking could be masking those of arsenic <sup>27, 40</sup>.

Strengths of this study include having American Indian reference values derived from the SHS cohort <sup>12</sup>. This is important as anthropomorphic differences vary between ethnic groups, and NHANES III, from which normative values are generated, did not include American Indians. The reference values allowed for results to be evaluated for abnormalities against predicted values for better interpretation of results. Other major

strengths include the community-based sample, standardized spirometry, and extensive data on potential confounders.

## **CONCLUSIONS**

Our study provides evidence of an association between low-moderate arsenic exposure and a spirometric restrictive pattern, airflow obstruction (especially based on the LLN), select respiratory symptoms, and higher self-reported emphysema. No other study has evaluated the association between arsenic exposure and individual spirometric lung function in American Indians, US population, or population exposed to low-moderate arsenic levels. Research in additional populations is needed to confirm the association, including evaluation of relevant subclinical and pathophysiological outcomes. This could include repeated urinary arsenic measurement and diagnostic testing, like computed tomography scan, to better assess patterns of lung disease.

## TABLES

**Table 1. Baseline (1998-1991) Participant Characteristics by Airflow Obstruction and Restrictive Pattern at Visit 2 (1993-1995) (N=2,132)**

	<b>Airflow obstruction</b> FEV1/FVC <0.70 (n= 458)	<b>Restrictive Pattern</b> FEV1/FVC >0.70 FVC <80% predicted (n=307)	<b>Healthy</b> FEV1/FVC >0.70 FVC >80% predicted (n=1367)
Age, years	59.2 (0.3)	56.1 (0.5)	54.5 (0.2)
Female	226 (49.3%)	206 (67.1%)	860 (62.9%)
Education			
No high school (HS)	122 (26.6%)	68 (21.1%)	187 (13.7%)
Some HS	111 (24.2%)	69 (22.4%)	313 (22.9%)
Completed HS or higher	225 (49.2%)	170 (55.4%)	867 (63.4%)
Smoking status			
Never	113 (24.7%)	109 (35.5%)	451 (33.0%)
Former	134 (29.3%)	91 (29.6%)	443 (32.4%)
Current	211 (46.1%)	107 (34.9%)	473 (34.6%)
Smoking pack years	18.2 (0.9)	9.2 (0.7)	8.2 (0.3)
BMI, kg/m <sup>2</sup>	29.0 (0.2)	33.0 (0.4)	31.4 (0.2)
Diabetes	168 (36.7%)	185 (60.3%)	539 (39.4%)
Urine $\Sigma$ As, $\mu$ g/g creatinine	11.1 (6.2 - 16.1)	12.0 (6.2-20.2)	9.5 (5.6-15.7)
iAs, %	8.5 (5.9 - 11.7)	7.6 (5.6-10.7)	7.7 (5.5-11.0)
MMA, %	14.7 (11.3-18.5)	12.8 (10.5-16.2)	13.8 (10.8-17.2)
FEV1, %predicted	77.7 (0.8)	73.6 (0.6)	100.2 (0.3)
FVC, %predicted	93.9 (0.8)	69.4 (0.5)	98.6 (0.3)
FEV1/FVC, %	62.2 (0.3)	81.4 (0.4)	78.2 (0.1)
Inhaled steroids	8 (1.7%)	8 (2.6%)	36 (2.6%)
Self-reported chronic bronchitis	59 (13.0%)	49 (16.1%)	112 (8.3%)
Self-reported emphysema	34 (7.5%)	19 (6.3%)	25 (1.8%)
Self-reported asthma	59 (13.1%)	40 (13.1%)	87 (6.4%)
Medical record tuberculosis	83 (18.1%)	54 (17.6%)	155 (11.3%)
Self-reported cough	140 (30.6%)	84 (27.5%)	252 (18.5%)
Cough 4-6x/week	92 (64.8%)	54 (63.5%)	158 (61.5%)
Phlegm	89 (62.2%)	51 (60.0%)	161 (59.9%)
Shortness of breath	221 (48.6%)	169 (57.1%)	585 (43.1%)
Stopping for breath	97 (41.8%)	72 (42.4%)	186 (31.3%)

All analyses are weighted. Data are mean (SE), n (% of column), or median (interquartile range)

\* $\mu$ g/g creatinine;  $\Sigma$ As = inorganic arsenic plus methylated species

**Table 2. Participant Characteristics by Baseline (1998-1991) Urinary Arsenic Concentration\* (N=2,132)**

	Inorganic Plus Methylated Arsenic Species $\mu\text{g/g}$ creatinine			P-value**
	Tertile 1 $\leq 7.0^*$	Tertile 2 7.1-13.9*	Tertile 3 $\geq 14.0^*$	
Age, years	55.6	55.6	56.0	0.37
Female	494 (56.0%)	443 (61.1%)	355 (67.6%)	<0.001
Education				<0.001
No high school (HS)	80 (9.1%)	149 (20.6%)	148 (28.2%)	
Some HS	202 (22.9%)	160 (22.1%)	131 (25.0%)	
Completed HS or higher	600 (68.0%)	416 (57.4%)	246 (46.9%)	
BMI, $\text{kg/m}^2$	30.8 (0.1)	31.3 (0.2)	31.6 (0.3)	0.01
Diabetes	317 (35.9%)	296 (40.8%)	279 (53.1%)	<0.001
Smoking status				0.06
Never	292 (33.9%)	214 (29.5%)	167 (31.8%)	
Former	288 (32.6%)	235 (32.4%)	145 (27.6%)	
Current	302 (34.2%)	276 (38.1%)	213 (40.5%)	
Smoking pack years	11.4 (0.4)	10.8 (0.4)	8.9 (0.5)	<0.001
FEV1, %predicted	92.8 (0.4)	92.5 (0.6)	88.7 (0.7)	<0.001
FVC, %predicted	93.3 (0.4)	95.0 (0.6)	90.3 (0.7)	<0.001
FEV1/FVC, %	76.1 (0.2)	74.9 (0.3)	75.6 (0.4)	0.21
Airflow obstruction $^\diamond$	157 (20.7%)	167 (26.3%)	134 (31.0%)	0.02
Restrictive pattern $^\ddagger$	125 (17.2%)	89 (15.9%)	93 (23.8%)	<0.001
Self-reported chronic bronchitis	82 (9.2%)	78 (10.8%)	60 (11.4%)	0.59
Self-reported emphysema	33 (3.7%)	26 (3.6%)	19 (3.6%)	0.43
Self-reported asthma	77 (8.8%)	65 (9.0%)	44 (8.4%)	0.51
Medical record tuberculosis	133 (15.1%)	99 (13.7%)	60 (11.4%)	0.02

All analyses are weighted. Data are mean (SE) or *n* (% of tertile)

\*Tertiles are range; calculated based on overall population; sum of inorganic and methylated species  $\mu\text{g/g}$  creatinine

\*\*For continuous variables, ANOVA was used to calculate p-value; for categorical variables, chi-square test was used

$^\diamond$  Fixed airflow obstruction: FEV1/FVC <0.70

$^\ddagger$  Restrictive pattern: FEV1/FVC >0.70 & FVC <80% predicted

**Table 3. Weighted Odds Ratio (95% Confidence Interval) of Airflow Obstruction and Restrictive Pattern, Defined Based on Fixed Ratios, by Urinary Arsenic Concentration\***

	Inorganic Plus Methylated Arsenic Species μg/g creatinine				P-trend**
	Tertile 1 ≤7.0*	Tertile 2 7.1-13.9*	Tertile 3 ≥14.0*	75 <sup>th</sup> vs. 25 <sup>th</sup> Percentile <sup>‡</sup>	
<b>Airflow obstruction<sup>†</sup>/ Healthy<sup>Ω</sup></b>	157/600	167/469	134/298	458/1367	
Model 1	1.00 (Ref)	1.15 (0.93, 1.43)	1.45 (1.10, 1.91)	1.27 (1.08, 1.51)	0.005
Model 2	1.00 (Ref)	1.11 (0.89, 1.39)	1.34 (1.01, 1.77)	1.21 (1.01, 1.43)	0.03
Model 3	1.00 (Ref)	1.12 (0.90, 1.40)	1.33 (0.99, 1.77)	1.17 (0.99, 1.38)	0.07
Model 4	1.00 (Ref)	1.12 (0.90, 1.41)	1.33 (0.99, 1.79)	1.17 (0.99, 1.40)	0.07
<b>Restrictive pattern<sup>a</sup>/ Healthy<sup>Ω</sup></b>	125/600	89/469	93/298	307/1367	
Model 1	1.00 (Ref)	0.92 (0.69, 1.23)	1.32 (0.92, 1.91)	1.25 (0.99, 1.57)	0.06
Model 2	1.00 (Ref)	0.91 (0.68, 1.22)	1.30 (0.90, 1.89)	1.23 (0.98, 1.55)	0.07
Model 3	1.00 (Ref)	0.92 (0.68, 1.23)	1.34 (0.92, 1.96)	1.27 (1.01, 1.60)	0.04
Model 4	1.00 (Ref)	0.88 (0.65, 1.19)	1.16 (0.78, 1.73)	1.18 (0.93, 1.50)	0.18

<sup>†</sup> Fixed airflow obstruction: FEV1/FVC <0.70

<sup>Ω</sup> Healthy: FEV1/FVC >0.70 & FVC >80% predicted

<sup>a</sup> Restrictive pattern: FEV1/FVC >0.70 & FVC <80% predicted

\*Tertiles are range; calculated based on overall population; sum of iAs, MMA, DMA μg/g creatinine

\*\*P-trend calculated modeling log-arsenic as continuous

<sup>‡</sup> Comparison of the 75<sup>th</sup> and 25<sup>th</sup> percentiles (interquartile range) of urinary arsenic concentrations (16.7 vs. 5.8 μg/g creatinine)

Model 1: adjusted for age, sex, education, site

Model 2: further adjusted for smoking status and smoking pack-year

Model 3: further adjusted for eGFR, tuberculosis, and BMI

Model 4: sensitivity analysis: further adjusted for diabetes

**Table 4. Weighted Odds Ratio (95% Confidence Interval) of Airflow Obstruction and Restrictive Pattern, Defined Based on the Lower Limit of Normal (LLN), by Urinary Arsenic Concentration\* (N= 2132)**

	Inorganic Plus Methylated Arsenic Species $\mu\text{g/g}$ creatinine				P-trend**
	Tertile 1 $\leq 7.0^*$	Tertile 2 7.1-13.9*	Tertile 3 $\geq 14.0^*$	75 <sup>th</sup> vs. 25 <sup>th</sup> Percentile <sup>‡</sup>	
<b>Airflow obstruction<sup>†</sup>/</b> <b>Healthy<sup>Ω</sup></b>	47/773	57/626	47/435	151/1,834	
Model 1	1.00 (Ref)	1.15 (0.84, 1.58)	1.64 (1.16, 2.34)	1.47 (1.17, 1.88)	0.001
Model 2	1.00 (Ref)	1.11 (0.80, 1.53)	1.50 (1.05, 2.15)	1.38 (1.09, 1.76)	0.007
Model 3	1.00 (Ref)	1.08 (0.78, 1.50)	1.36 (0.94, 1.97)	1.28 (1.02, 1.60)	0.03
Model 4	1.00 (Ref)	1.07 (0.78, 1.49)	1.33 (0.92, 1.93)	1.26 (1.01, 1.59)	0.04
<b>Restrictive pattern<sup>a</sup>/</b> <b>Healthy<sup>Ω</sup></b>	62/773	42/626	43/435	147/1,834	
Model 1	1.00 (Ref)	0.85 (0.58, 1.26)	1.45 (0.91, 2.30)	1.33 (1.00, 1.76)	0.05
Model 2	1.00 (Ref)	0.85 (0.58, 1.26)	1.41 (0.88, 2.25)	1.30 (0.98, 1.74)	0.07
Model 3	1.00 (Ref)	0.86 (0.58, 1.28)	1.42 (0.88, 2.28)	1.33 (0.90, 1.50)	0.06
Model 4	1.00 (Ref)	0.83 (0.56, 1.23)	1.23 (0.76, 2.00)	1.21 (0.90, 1.64)	0.22

<sup>†</sup> Airflow obstruction: FEV1/FVC <LLN

<sup>a</sup> Restrictive pattern: FEV1/FVC >LLN & FVC <LLN

<sup>Ω</sup> Healthy: FEV1/FVC >LLN and FVC >LLN

\*Tertiles are range; calculated based on overall population; sum of iAs, MMA, DMA  $\mu\text{g/g}$  creatinine

\*\*P-trend calculated modeling log-arsenic as continuous

<sup>‡</sup> Comparison of the 75<sup>th</sup> and 25<sup>th</sup> percentiles (interquartile range) of urinary arsenic concentrations (16.7 vs. 5.8  $\mu\text{g/g}$  creatinine)

Model 1: adjusted for age, sex, education, site

Model 2: further adjusted for smoking status and smoking pack-year

Model 3: further adjusted for eGFR, tuberculosis, and BMI

Model 4: sensitivity analysis: further adjusted for diabetes

**Table 5. Weighted Mean Difference (95% Confidence Interval) of Lung Function at Visit 2 (1993-1995) by Urinary Arsenic Concentration\* at Baseline (1989-1991)**

	N	Inorganic Plus Methylated Arsenic Species µg/g creatinine				P-trend**
		Tertile 1 ≤7.0*	Tertile 2 7.1-13.9*	Tertile 3 ≥14.0*	75 <sup>th</sup> vs. 25 <sup>th</sup> Percentile <sup>‡</sup>	
<b>FEV1, % predicted</b>						
All	2132	0 (Ref)	0.92 (-0.52, 2.37)	-1.64 (-3.60, 0.32)	-1.39 (-2.51, -0.25)	0.02
Healthy <sup>a</sup>	1367	0 (Ref)	0.67 (-0.86, 2.19)	-0.49 (-2.58, 1.61)	0.85 (0.27, 2.74)	0.80
<b>FVC, % predicted</b>						
All	2132	0 (Ref)	2.09 (0.72, 3.47)	-1.01 (-2.85, 0.83)	-1.13 (-2.21, -0.05)	0.04
Healthy <sup>a</sup>	1367	0 (Ref)	1.15 (-0.23, 2.53)	-0.73 (-2.60, 1.14)	0.70 (0.24, 2.02)	0.50
<b>FEV1/FVC (%)</b>						
All	2132	0 (Ref)	-0.62 (-1.26, 0.002)	-0.16 (-1.01, 0.69)	0.09 (-0.46, 0.66)	0.74
Healthy <sup>a</sup>	1367	0 (Ref)	-0.31 (-0.85, 0.25)	0.26 (-0.49, 1.01)	1.21 (0.76, 1.94)	0.42
<b>FEV1, mL</b>						
All	2132	0 (Ref)	0.007 (-0.04, 0.06)	-0.09 (-0.15, -0.03)	-0.07 (-0.11, -0.03)	<0.001
Healthy <sup>a</sup>	1367	0 (Ref)	0.003 (-0.05, 0.06)	-0.06 (-0.14, 0.01)	-0.03 (-0.07, -0.003)	0.07
<b>FVC, mL</b>						
All	2132	0 (Ref)	0.06 (-0.004, 0.11)	-0.10 (-0.17, -0.02)	-0.07 (-0.12, -0.03)	0.001
Healthy <sup>a</sup>	1367	0 (Ref)	0.02 (-0.05, 0.09)	-0.09 (-0.19, -0.0001)	-0.05 (-0.10, -0.004)	0.03

<sup>a</sup> Healthy: FEV1/FVC >0.70 & FVC >80% predicted

Adjusted for age, sex, education, site, smoking status, smoking pack-year, eGFR, tuberculosis, and BMI

\*Tertiles are range; calculated based on overall population; sum of inorganic and methylated species µg/g creatinine

<sup>‡</sup> Comparison of the 75<sup>th</sup> and 25<sup>th</sup> percentiles (interquartile range) of the sum inorganic and methylated urinary arsenic concentrations (16.7 vs. 5.8 µg/g creatinine)

\*\*P-trend calculated modeling log-arsenic as continuous

**Table 6. Weighted Odds Ratio (95% Confidence Interval) of Respiratory Symptom by Urinary Arsenic Concentration (N=2,132)**

	Inorganic Plus Methylated Arsenic Species µg/g creatinine				P-trend <sup>Ω</sup>
	Tertile 1 ≤7.0*	Tertile 2 7.1-13.9*	Tertile 3 ≥14.0*	75 <sup>th</sup> vs. 25 <sup>th</sup> Percentile	
<b>Cough**/No cough</b>	191/690	169/555	116/406	476/1651	
Model 1	1.00 (Ref)	0.87 (0.70, 1.09)	0.69 (0.51, 0.93)	0.82 (0.69, 0.98)	0.03
Model 2	1.00 (Ref)	0.86 (0.69, 1.06)	0.64 (0.48, 0.87)	0.79 (0.66, 0.93)	0.006
Model 3	1.00 (Ref)	0.84 (0.68, 1.05)	0.63 (0.47, 0.86)	0.78 (0.65, 0.93)	0.005
Model 4	1.00 (Ref)	0.84 (0.68, 1.05)	0.63 (0.46, 0.85)	0.77 (0.65, 0.92)	0.004
<b>Cough 4-6x per day<sup>Δ</sup>/No</b>	114/768	111/614	79/446	304/1828	
Model 1	1.00 (Ref)	0.97 (0.73, 1.28)	0.86 (0.59, 1.26)	0.96 (0.78, 1.18)	0.71
Model 2	1.00 (Ref)	0.94 (0.71, 1.24)	0.79 (0.54, 1.16)	0.91 (0.73, 1.12)	0.36
Model 3	1.00 (Ref)	0.94 (0.71, 1.25)	0.80 (0.54, 1.17)	0.92 (0.74, 1.13)	0.44
Model 4	1.00 (Ref)	0.94 (0.71, 1.25)	0.81 (0.55, 1.18)	0.93 (0.75, 1.15)	0.48
<b>Phlegm<sup>†</sup>/No</b>	117/765	114/611	70/455	301/1831	
Model 1	1.00 (Ref)	1.19 (0.95, 1.49)	1.06 (0.77, 1.47)	1.09 (0.90, 1.31)	0.37
Model 2	1.00 (Ref)	1.16 (0.93, 1.46)	0.99 (0.71, 1.37)	1.03 (0.86, 1.25)	0.71
Model 3	1.00 (Ref)	1.18 (0.94, 1.49)	1.01 (0.73, 1.41)	1.05 (0.87, 1.27)	0.57
Model 4	1.00 (Ref)	1.18 (0.94, 1.48)	1.01 (0.72, 1.40)	1.05 (0.87, 1.27)	0.59
<b>Shortness of breath<sup>‡</sup>/No</b>	369/503	363/355	243/275	975/1133	
Model 1	1.00 (Ref)	1.16 (0.98, 1.37)	0.90 (0.72, 1.13)	1.02 (0.88, 1.17)	0.81
Model 2	1.00 (Ref)	1.16 (0.98, 1.37)	0.88 (0.70, 1.11)	1.00 (0.87, 1.15)	0.97
Model 3	1.00 (Ref)	1.17 (0.98, 1.39)	0.93 (0.73, 1.18)	1.08 (0.93, 1.23)	0.34
Model 4	1.00 (Ref)	1.18 (0.99, 1.40)	0.94 (0.74, 1.20)	1.08 (0.94, 1.25)	0.28
<b>Stop for breath<sup>§</sup>/No</b>	101/781	151/574	103/422	355/1777	
Model 1	1.00 (Ref)	1.67 (1.35, 2.07)	1.56 (1.18, 2.06)	1.33 (1.11, 1.59)	0.002
Model 2	1.00 (Ref)	1.66 (1.34, 2.05)	1.52 (1.14, 2.01)	1.30 (1.08, 1.55)	0.005
Model 3	1.00 (Ref)	1.76 (1.42, 2.19)	1.68 (1.26, 2.24)	1.41 (1.19, 1.69)	<0.001
Model 4	1.00 (Ref)	1.76 (1.41, 2.19)	1.64 (1.23, 2.20)	1.40 (1.17, 1.67)	<0.001

Model 1: adjusted for age, sex, education, site

Model 2: further adjusted for smoking status and smoking pack-year

Model 3: further adjusted for eGFR, tuberculosis, and BMI

Model 4: sensitivity analysis: further adjusted for diabetes

\*Tertiles are range; calculated based on overall population; sum of inorganic and methylated species µg/g creatinine

<sup>Ω</sup>P-trend calculated modeling log-arsenic as continuous

\*\*Do you usually have a cough?

<sup>Δ</sup>Do you usually cough as much as 4-6 times/day, 4 or more days/week?

<sup>†</sup>Do you usually bring up phlegm when you cough?

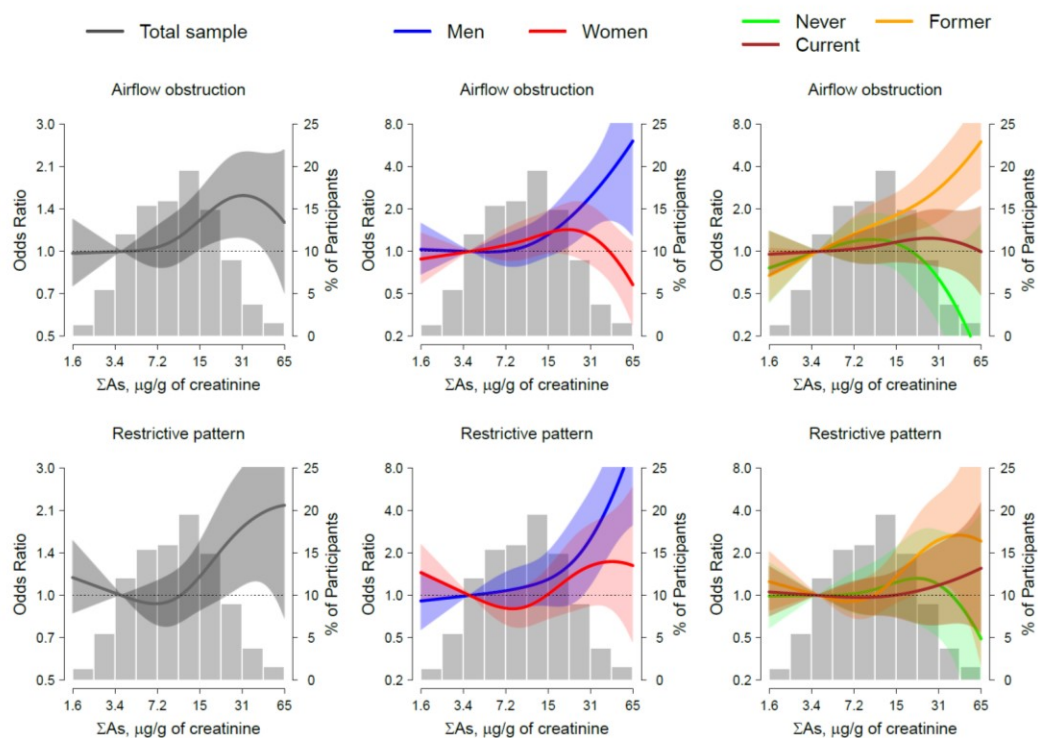
<sup>‡</sup>Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?

<sup>§</sup>Do you ever have to stop for breath while walking about 100 yards or a few minutes on the level?

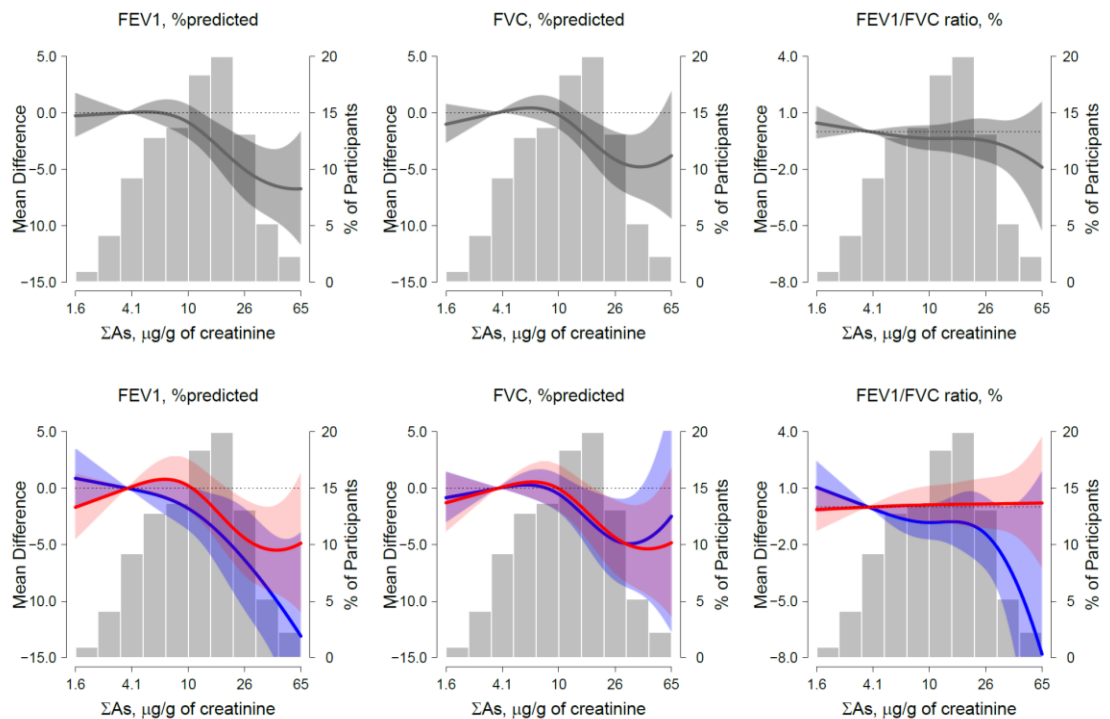


## FIGURES

**Figure 1. Dose-Response Relationship of Fixed Airflow Obstruction and Restrictive Patterns with Urinary Arsenic Concentrations.** Solid lines and shaded areas surrounding the lines represent the weighted odds ratio and 95% confidence intervals of airflow obstruction (upper panels) and restrictive pattern (lower panels). Models were conducted in the total study sample (left panels), stratified by sex (middle panels), and stratified by smoking status (right panels). These models were adjusted for age, sex (except models stratified by sex), education, study site, smoking status (except models stratified by smoking status), smoking pack-year, eGFR, tuberculosis and BMI. Histograms in the background and right Y axis represent the distribution of urinary arsenic. The histograms were truncated by excluding 10 participants with urine arsenic concentrations above 65  $\mu\text{g/g}$  of creatinine.



**Figure 2. Dose-Response Relationship of Lung Function at Visit 2 (1993 – 1995) with Urinary Arsenic Concentrations.** Solid lines and shaded areas surrounding the lines represent the weighted mean differences and 95% confidence intervals of FEV1 % predicted (right panels), FVC % predicted (middle panels), and FEV1/FVC (right panels). Models were conducted in the total study sample (upper panels) and stratified by sex (lower panels). These models were adjusted for age, sex (except models stratified by sex), education, study site, smoking status, smoking pack-year, eGFR, tuberculosis and BMI. Histograms in the background and right Y axis represent the distribution of urinary arsenic. The histograms were truncated by excluding 10 participants with urine arsenic concentrations above 65  $\mu\text{g/g}$  of creatinine.



## SUPPLEMENTAL MATERIAL

**Supplement table 1S. Sensitivity Analysis: adjustment for diabetes. Weighted Mean Difference (95% Confidence Interval) of Lung Function at Visit 2 (1993-1995) by Urinary Arsenic Concentration\* at Baseline (1989-1991)**

N		Inorganic Plus Methylated Arsenic Species µg/g creatinine				P-trend**
		Tertile 1 ≤7.0*	Tertile 2 7.1-13.9*	Tertile 3 ≥14.0*	75 <sup>th</sup> vs. 25 <sup>th</sup> Percentile‡	
<b>FEV1, % predicted</b>						
All	2132	0 (Ref)	0.91 (-0.56, 2.39)	-1.44 (-3.44, 0.56)	-1.28 (-2.39, -0.17)	0.02
Healthy <sup>a</sup>	1367	0 (Ref)	0.67 (-0.86, 2.20)	-0.47 (-2.60, 2.20)	0.87 (0.27, 2.80)	0.82
<b>FVC, % predicted</b>						
All	2132	0 (Ref)	2.16 (0.77, 3.56)	-0.54 (-2.41, 1.34)	-0.85 (-1.91, 0.22)	0.12
Healthy <sup>a</sup>	1367	0 (Ref)	1.20 (-0.20, 2.59)	-0.49 (-2.40, 1.43)	0.79 (0.27, 2.32)	0.67
<b>FEV1/FVC (%)</b>						
All	2132	0 (Ref)	-0.70 (-1.36, -0.05)	-0.36 (-1.23, 0.52)	-0.01 (-0.58, 0.55)	0.97
Healthy <sup>a</sup>	1367	0 (Ref)	-0.35 (-0.89, 0.20)	0.08 (-0.66, 0.81)	1.10 (0.69, 1.74)	0.68

<sup>a</sup> Healthy: FEV1/FVC >0.70 & FVC >80% predicted

Adjusted for age, sex, education, site, smoking status, smoking pack-year, eGFR, tuberculosis, BMI, and diabetes

\*Tertiles are range; calculated based on overall population; sum of inorganic and methylated species µg/g creatinine

<sup>‡</sup> Comparison of the 75<sup>th</sup> and 25<sup>th</sup> percentiles (interquartile range) of the sum inorganic and methylated urinary arsenic concentrations (16.7 vs. 5.8 µg/g creatinine)

\*\*P-trend calculated modeling log-arsenic as continuous

**Supplemental table 2S. Weighted Odds Ratios (95% Confidence Interval) for Airflow Obstruction and Restrictive Pattern, Defined Based on Fixed Ratios, when an Interquartile Range\* of Urinary Arsenic Concentration is Compared, by Participant Characteristics at Baseline**

Variable	Airflow obstruction <sup>a</sup> FEV1/FVC <0.70				Restrictive pattern <sup>a</sup> FEV1/FVC >0.70 & FVC <80% predicted			
	N	Odds Ratio	95% CI	P for interaction**	N	Odds Ratio	95% CI	P for interaction**
Sex				0.003				0.82
Male	739	1.47	(1.07, 2.06)		608	1.10	(0.69, 1.76)	
Female	1086	1.07	(0.82, 1.33)		1066	1.23	(0.90, 1.69)	
Age <sup>‡</sup> , years				0.52				0.43
<55.7	977	1.31	(1.01, 1.71)		965	1.30	(0.91, 1.86)	
≥55.7	848	1.12	(0.85, 1.47)		709	1.06	(0.74, 1.54)	
Smoking status				0.12				0.03
Never	564	0.88	(0.57, 1.37)		560	0.99	(0.60, 1.64)	
Former	577	1.74	(1.20, 2.55)		534	1.34	(0.82, 2.17)	
Current	684	1.10	(0.81, 1.51)		580	1.16	(0.79, 1.73)	
BMI, kg/m <sup>2</sup>				0.15				0.31
<25	317	1.51	(0.99, 2.29)		220	0.91	(0.39, 2.11)	
≥25 - <30	646	1.29	(0.93, 1.78)		578	1.67	(1.09, 2.57)	
≥30	862	0.89	(0.62, 1.29)		876	1.04	(0.72, 1.51)	
Diabetes				0.84				0.60
Yes	707	1.05	(0.71, 1.57)		724	1.17	(0.82, 1.69)	
No	1,118	1.23	(0.99, 1.54)		950	1.08	(0.74, 1.59)	

\*Interquartile range of the sum inorganic and methylated urinary arsenic concentrations was 5.8 to 16.7 µg/g creatinine

<sup>a</sup> Compared to Healthy: FEV1/FVC >0.70 & FVC >80% predicted

\*\*ORs were stratified by each subgroup of interest, and associated *P* values for interaction were obtained from models with interaction terms and using Wald tests for multiple coefficients

Models were adjusted for sex, age, education, site, smoking status, cigarette pack-years, body mass index, estimated glomerular filtration rate, and tuberculosis.

<sup>‡</sup> Mean age.

**Supplemental table 3S. Weighted Odds Ratio (95% Confidence Interval) of Self-reported Emphysema, Chronic Bronchitis, or Asthma by Urine Arsenic Tertile Concentration**

	Inorganic Plus Methylated Arsenic Species µg/g creatinine			75 <sup>th</sup> vs. 25 <sup>th</sup> Percentile <sup>‡</sup>	P-trend**
	Tertile 1 ≤7.0*	Tertile 2 7.1-13.9*	Tertile 3 ≥14.0*		
<b>Chronic Bronchitis /None</b> (N=2,116)	82/797	78/638	60/461	220/1896	
Model 1	1.00 (Ref)	1.15 (0.85, 1.56)	1.19 (0.79, 1.81)	1.13 (0.90, 1.44)	0.29
Model 2	1.00 (Ref)	1.14 (0.84, 1.54)	1.16 (0.76, 1.75)	1.11 (0.88, 1.40)	0.37
Model 3	1.00 (Ref)	1.14 (0.84, 1.56)	1.20 (0.79, 1.83)	1.16 (0.92, 1.47)	0.22
Model 4	1.00 (Ref)	1.14 (0.84, 1.55)	1.17 (0.76, 1.79)	1.15 (0.90, 1.46)	0.27
<b>Emphysema/None</b> (N=2,116)	33/847	26/692	19/499	78/2038	
Model 1	1.00 (Ref)	1.23 (0.88, 1.74)	2.04 (1.35, 3.08)	1.76 (1.38, 2.27)	<0.001
Model 2	1.00 (Ref)	1.18 (0.83, 1.67)	1.79 (1.16, 2.77)	1.64 (1.27, 2.09)	<0.001
Model 3	1.00 (Ref)	1.18 (0.83, 1.67)	1.83 (1.18, 2.83)	1.66 (1.29, 2.15)	<0.001
Model 4	1.00 (Ref)	1.17 (0.82, 1.66)	1.79 (1.16, 2.78)	1.66 (1.27, 2.13)	<0.001
<b>Asthma/None</b> (N=2,117)	77/800	65/653	44/478	186/1931	
Model 1	1.00 (Ref)	0.91 (0.67, 1.25)	0.61 (0.40, 0.94)	0.76 (0.60, 0.96)	0.02
Model 2	1.00 (Ref)	0.90 (0.66, 1.23)	0.60 (0.39, 0.93)	0.75 (0.60, 0.95)	0.02
Model 3	1.00 (Ref)	0.90 (0.66, 1.23)	0.61 (0.40, 0.95)	0.76 (0.60, 0.96)	0.02
Model 4	1.00 (Ref)	0.90 (0.66, 1.24)	0.63 (0.41, 0.97)	0.77 (0.61, 0.98)	0.03

\*Tertiles are range; calculated based on overall population; sum of inorganic and methylated species µg/g creatinine

\*\*P-trend calculated modeling log-arsenic as continuous

Model 1: adjusted for age, sex, education, site

Model 2: further adjusted for smoking status and smoking pack-year

Model 3: further adjusted for eGFR, tuberculosis, and BMI

Model 4: sensitivity analysis: further adjusted for diabetes

**Supplemental table 4S. Weighted Odds Ratio (95% Confidence Interval) of Airflow Obstruction and Restrictive Pattern, Defined Based on Fixed Ratios, by 5% Change in Urinary Arsenic Metabolites\***

	%iAs	%MMA	%DMA
<b>Airflow obstruction/Healthy</b> (439/1,282)			
Model 3	1.04 (0.93, 1.15)	0.92 (0.83, 1.02)	1.02 (0.96, 1.09)
Model 4	1.04 (0.93, 1.15)	0.92 (0.83, 1.02)	1.04 (0.93, 1.15)
<b>Restrictive pattern/Healthy</b> (280/1,282)			
Model 3	0.95 (0.81, 1.12)	0.88 (0.77, 1.00)	1.07 (0.98, 1.17)
Model 4	0.94 (0.80, 1.11)	0.93 (0.81, 1.07)	1.05 (0.96, 1.14)

\*sum of inorganic and methylated species  $\mu\text{g/g}$  creatinine

Airflow obstruction: FEV1/FVC <0.70

Healthy: FEV1/FVC >0.70 & FVC >80% predicted

Restrictive pattern: FEV1/FVC >0.70 & FVC <80% predicted

Model 3: adjusted for age, sex, education, site, smoking status, smoking pack-year, eGFR, tuberculosis, and BMI

Model 4: sensitivity analysis: further adjusted for diabetes

## CHAPTER 2

### Lung Function and Respiratory Symptoms after Tuberculosis in an American Indian Population: The Strong Heart Study

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## ABSTRACT

**Background:** Permanent lung function impairment after active tuberculosis infection is relatively common. It remains unclear which spirometric pattern is most prevalent after tuberculosis. Our objective was to elucidate the impact of active tuberculosis survival on lung health in the Strong Heart Study, a population of American Indians historically highly impacted by tuberculosis. As arsenic exposure has also been related to lung function in the Strong Heart Study, we also assessed the joint effect between arsenic exposure and past active tuberculosis.

**Methods:** The Strong Heart Study is an ongoing population-based, prospective study of cardiovascular disease and its risk factors in American Indian adults. This study uses tuberculosis data and spirometry data from the Visit 2 examination (1993-1995). Prior active tuberculosis was ascertained by a review of medical records. FVC, FEV1, and FEV1/FVC were measured by spirometry. An additional analysis was conducted to evaluate the potential association between active tuberculosis and arsenic exposure.

**Results:** A history of active tuberculosis was associated with reduced percent predicted FVC and FEV1, an increased odds of airflow obstruction (odds ratio 1.45, 95% CI 1.08, 1.95), and spirometric restrictive pattern (odds ratio 1.73, 95% CI 1.24, 2.40). These associations persisted after adjustment for diabetes and other risk factors, including smoking. We also observed the presence of cough, phlegm, and exertional dyspnea after a history of active tuberculosis. In the additional analysis, increasing urinary arsenic concentrations were associated with decreasing lung function in those with a history of active tuberculosis, but a reduced odds of active tuberculosis was found with elevated arsenic.



**Conclusions:** Our findings support existing knowledge that a history of active tuberculosis is a risk factor for long-term respiratory impairment. Arsenic exposure, although inversely associated with prior active tuberculosis, was associated with a further decrease in lung function among those with a prior active tuberculosis history. The possible interaction between arsenic and tuberculosis, as well as the reduced odds of tuberculosis associated with arsenic exposure, warrants further investigation, as many populations at risk of developing active tuberculosis are also exposed to arsenic-contaminated water.

## INTRODUCTION

Tuberculosis, a preventable and treatable infectious disease when drug therapies are successful, largely affects vulnerable populations, including indigenous peoples, such as American Indians. Worldwide, indigenous populations are at a higher risk of tuberculosis than non-indigenous populations due to a higher than average prevalence of predisposing risk factors, including diabetes, smoking, and socioeconomic circumstances.<sup>1</sup> Historically, tuberculosis was an important cause of mortality in American Indians, with peak disease likely around 1910.<sup>2</sup> Even as mortality, morbidity, and risk of infection from tuberculosis have greatly decreased among American Indians, incidence rates remain above that of the non-foreign born non-Hispanic White population.<sup>1,3</sup>

A recent systematic review found that pulmonary impairment is relatively common among those with a history of tuberculosis.<sup>4</sup> Even after microbiologic cure of the infectious disease, tuberculosis can be associated with long-term pulmonary damage, and this impairment, which can involve airflow obstruction and/or spirometric restrictive pattern defects,<sup>4</sup> contributes to an unmeasured burden of chronic lung disease.<sup>5,6</sup>

In this study, we evaluated the relationship between a history of active tuberculosis and subsequent lung function in American Indians participating in the Strong Heart Study (SHS), a population-based study that represents Tribal Nations across four states in the United States (US). We assessed this association using data from a medical record-based history of active tuberculosis, spirometric measurements, and self-reported respiratory symptoms.

We also conducted an additional analysis to evaluate the potential association between tuberculosis and arsenic. In the US, elevated exposure to arsenic disproportionately affects populations relying on private well water. This includes many American Indian communities where naturally occurring arsenic is often above 10 µg/L, the current US Environmental Protection Agency (EPA) safety standard. In the SHS population, arsenic levels in drinking water were stable and relatively high before 2006, when new water systems were introduced in some of the communities to comply with the US EPA safety standard. For decades, participants were thus exposed to relatively high arsenic exposure levels.<sup>7</sup> At present, one study found high arsenic exposure associated with higher tuberculosis mortality in Chile.<sup>8</sup> In the SHS cohort, low-moderate arsenic exposure (<100 µg/L), which is widely prevalent in study communities,<sup>7</sup> was positively associated with a spirometric restrictive pattern, airflow obstruction, and lower lung function, independent of active tuberculosis history (under review). There is also prior knowledge that arsenic is an immunosuppressant.<sup>9,10</sup> Given these previous findings, we examined whether a history of active tuberculosis was associated with arsenic exposure and possible interaction between arsenic and tuberculosis on lung disease.

The SHS provides a unique opportunity to examine the lung health of participants who have been previously treated for active tuberculosis, allowing for the assessment of this burden compared to community members not affected by active tuberculosis, in a population-based study. We undertook this study to characterize the association of an active tuberculosis diagnosis on long-term functional pulmonary impairment in an American Indian population.

## **METHODS**

### **Study population**

The SHS is an ongoing, population-based, prospective study of cardiovascular disease and its risk factors in American Indian adults. The SHS recruited 4,549 residents of Tribal Nations located in Arizona (AZ), Oklahoma (OK), and North Dakota and South Dakota (ND/SD) in the US. Study enrollment rates of eligible participants were 71.8% in AZ, 61.5% in OK, and 55.3% in ND/SD.<sup>11</sup> All men and women aged 45 to 74 years at the baseline visit in 1989-1991 were invited to participate. Compared with nonparticipants, participants were similar in age, body mass index, and diabetes status, and were more likely to be female.<sup>11</sup> Participants were invited to subsequent clinical visits between 1993-1995 and 1998-1999.<sup>12</sup>

This study uses tuberculosis data and spirometry data from the Visit 2 examination (1993-1995), available in 2,625 participants. We further excluded 123 participants missing data on cigarette pack-years, 33 participants missing diabetes status, and 36 missing body mass index (BMI) and waist circumference, leaving 2,463 individuals for this study.

### **Data collection**

Visit 1 (1989-1991) and Visit 2 (1993-1995) included biospecimen collection, a physical exam, and an interviewer-administered standardized questionnaire. Visits were performed by trained and certified examiners; methods have been previously described.<sup>12</sup>

### **Tuberculosis**

At Visit 2, a medical record review for a history of active and treated tuberculosis (class III tuberculosis) was performed. Case definition for class III tuberculosis involved having a positive culture for *Mycobacterium tuberculosis* from a body fluid or tissue or having a clinical picture suggestive of tuberculosis that responded to treatment with antitubercular medications. If any of those criteria were identified on a discharge diagnosis or on a problem list, they were considered to have a history of active tuberculosis. How the individual met the case definition, positive culture vs. response to treatment, was not available. If there was uncertainty about whether the lab results met the case definition, the medical record was reviewed by Dr. Tom Welty, co-author of this study. Dr. Welty, a retired physician from the US Indian Health Service and expert in clinical tuberculosis, developed the SHS data collection protocol and oversaw data collection and the identification of active tuberculosis based on available data in medical records at Visit 2. Participants received the diagnosis of active tuberculosis several years before the study visit (median (IQR) for the year of diagnosis was 1968 (1955-1979)).

Tuberculosis status was specifically added to the SHS Visit 2 research protocol to establish prevalence of tuberculin positivity, refer study participants with positive tuberculin tests to Indian Health Service for appropriate evaluation and treatment, and establish a prevalence of history of active tuberculosis. A history of an active tuberculosis diagnosis was not differentiated between pulmonary or extra pulmonary.

### **Spirometry for Identification of Airflow Obstruction and Restrictive Pattern**

Spirometry was performed by centrally trained and certified nurses and technicians at Visit 2.<sup>13</sup> Pre-bronchodilator testing was conducted in the sitting position,

except for participants with BMI >27 kg/m<sup>2</sup> who stood. Maneuvers were considered acceptable according to then-current American Thoracic Society recommendations; methods have been previously described.<sup>13, 14</sup>

Spirometric measurements of forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and their ratio (FEV1/FVC) were used in analyses. Reference values to determine the normal range of spirometry results for SHS participants were derived previously,<sup>13</sup> yielding FVC % predicted and FEV1 % predicted. Airflow obstruction was defined two ways: 1) by a fixed ratio (FEV1/FVC<0.70) using crude FEV1 and FVC values,<sup>15</sup> and 2) by the LLN (lower limit of normal), (FEV1/FVC <LLN), which classifies the bottom 5% of the ‘healthy’ population as abnormal (for the SHS, negative predictors of FEV1 were used to exclude participants from the healthy subset).<sup>13</sup> Spirometric based restrictive pattern was defined two ways: 1) as a low FVC (FVC<80 % predicted) together with a preserved ratio (FEV1/FVC≥0.70),<sup>16</sup> and 2) as the LLN (FEV1/FVC ≥LLN and FVC <LLN). Normal spirometry was defined as those with no-obstruction and no-restriction (fixed-ratio defined: FEV1/FVC≥0.70 and FVC>80 % predicted; LLN-defined: FEV1/FVC ≥LLN and FVC >LLN).

### **Symptoms and Lung Disease**

At Visit 2, participants were asked to report respiratory symptoms, including the presence of cough, frequent cough, cough with phlegm, shortness of breath when walking up a slight hill, and stopping for breath while walking 100 yards (see Table 5).

### **Urine arsenic**

Morning spot urine samples collected during the baseline visit were used to measure arsenic species (inorganic arsenic (iAs), methylarsonate (MMA), and dimethylarsinate (DMA)) using high performance liquid chromatography/inductively coupled plasma-mass spectrometry.<sup>12</sup> Quality control and quality assurance methods and laboratory procedures for urine arsenic analysis were conducted in 2009-2010 using highly precise laboratory methods that are still state-of-the-art today.<sup>17</sup> We used the sum of inorganic and methylated arsenic species (iAs+MMA+DMA) as the biomarker of exposure to inorganic arsenic in drinking water and food. Arsenobetaine levels were low, confirming that seafood intake is rare in the population. Urine creatinine was measured by an automated alkaline picrate methodology run on a rapid flow analyzer. To account for urine dilution in spot urine samples, urine arsenic ( $\mu\text{g/L}$ ) was divided by urine creatinine concentrations ( $\text{g/L}$ ) and the concentrations of total urine arsenic and its species were expressed in  $\mu\text{g/g}$  creatinine.

### **Other variables**

Models were progressively adjusted for relevant lung health variables to correct for potential confounding, using data from Visit 2. In model 1, we adjusted for age, sex, education, and study site, potential demographic confounders. In our study population, arsenic levels in drinking water are higher in AZ, lower in OK, and intermediate in ND and SD, yet levels still overlap across sites, allowing us to adjust for site. Education is associated with arsenic exposure in our study, mostly related to the fact that those in AZ have on average a lower education level. In model 2, we adjusted for smoking status and cigarette pack-year, a well-established risk factor for lung disease, with smoking status

categorized as never, former (smoked  $\geq 100$  cigarettes but no longer smoking), or current (smoking at then-present day). In model 3, we adjusted for body mass index, waist circumference and percent body fat to account for adiposity impact on respiratory system compliance.<sup>18, 19</sup> In model 4, we adjusted for diabetes, a highly prevalent risk factor found in the SHS cohort. Diabetes was defined as a fasting glucose level of  $\geq 126$  mg/dL, a 2-hour post-load plasma glucose level of  $\geq 200$  mg/dL, an HbA1c level of  $\geq 6.5\%$ , or use of an oral hypoglycemic agent or insulin.<sup>20</sup> To minimize any missing data, if Visit 2 data was missing for an individual, then baseline measurement was used (waist circumference: n= 5; body fat: n= 34; cigarette pack-years: n= 279; smoking status: n= 63).

### **Statistical analysis**

We conducted descriptive statistics to evaluate differences in participant demographic and lifestyle variables by tuberculosis status and by obstruction/restrictive spirometry-based pattern. We used logistic regression to estimate the odds ratio [OR] for presence of obstruction/restrictive pattern and respiratory symptoms by tuberculosis status, and linear regression to assess the mean difference of spirometric measurements by tuberculosis status. Effect modification of the association between active tuberculosis and lung outcomes was evaluated in fully adjusted models by including an interaction term for active tuberculosis status with indicator variables for sex (male/female), age ( $<59.9$  years/  $\geq 59.9$ ), smoking status (never/ former/ current), BMI ( $<25$  kg/m<sup>2</sup>/  $\geq 25$  -  $<30$ /  $\geq 30$ ), diabetes (yes/no), and arsenic (tertile:  $\leq 6.0$ , 6.1-11.9,  $\geq 12.0$ ,  $\mu\text{g/g}$ ). *P* values for interactions were obtained using Wald test for multiple coefficients. For the additional analysis, we estimated the odds ratio of active tuberculosis by urinary arsenic modeled as



a categorical variable, comparing tertiles of arsenic exposure, and as a continuous variable to compare an IQR increase of log urinary arsenic. *P* values for trend were obtained from modelling log-arsenic as continuous. All analyses were performed using Stata software, version 15.1 (College Station, Texas, USA) and figures were made in R ([www.r-project.org](http://www.r-project.org)).

## RESULTS

Fourteen percent of participants (344/2,463) had a history of active tuberculosis. Participants with a history of active tuberculosis were more likely to be older (mean [IQR]) (60.8 [55.5 – 66.8] years vs. 58.5 [53.0 – 65.3] years) and completed a lower level of education (no high school: 19.5% vs. 16.8%) (Table 1) compared to those without active tuberculosis. Those with versus those without a history of active tuberculosis had a lower FEV1 % predicted (mean [IQR]) (88.5 [75.5 – 100.7] vs. 94.1 [82.2 – 104.8]), FVC % predicted (91.1 [78.3 – 100.7] vs. 94.4 [83.3 – 105.3]), and FEV1/FVC% (75.6 [69.0 – 80.6] vs. 76.7 [71.5 – 80.1]). Those with a history of active tuberculosis were more likely to report presence of usual cough, frequent cough, production of phlegm with cough, and needing to stop for breath while walking for a few minutes (Table 1).

Using the fixed-ratio definition ( $FEV1/FVC < 0.70$ ), airway obstruction was present in 21.2% (521/2,463) overall (Table 2) and in 27.3% of those with active tuberculosis history (Table 1). A spirometric based restrictive pattern was present in 15.0% (369/2,463) overall and in 18.6% of those with active tuberculosis; the prevalence of diabetes in those with restriction was 68.0% (Table 2). Using the lower limit of normal

definition ( $FEV1/FVC < LLN$ ), obstruction was present in 6.7% (141/2,463) overall and in 9.6% of those with active tuberculosis; spirometric restriction was present in 7.0% (148/2,463) overall and in 8.7% of those with active tuberculosis (Table 1).

After full adjustment (Table 3, model 3), the odds ratio [95% CI] comparing those with a history of active tuberculosis to those without was 1.45 [1.08, 1.95] for obstruction and 1.73 [1.24, 2.40] for spirometric restrictive pattern (Table 3). When the lower limit of normal definition was used, the OR for was non-significant for obstruction (1.24 [0.81, 1.89]) and non-significant for spirometric restrictive pattern (1.47 [0.97, 2.29]) (Table 3), although the direction of the association was consistent with the findings based on the fixed ratio definitions.

The mean difference [95% CI] for FEV1 % predicted comparing active tuberculosis cases to those free of active tuberculosis was -5.84 [-7.91, -3.77]. For FVC % predicted, the mean difference was -5.23 [-7.45, -3.39] (Table 4). Amongst the normal group ( $FEV1/FVC > 0.70$  &  $FVC > 80\%$  predicted), both FEV1 % predicted and FVC % predicted remained significantly reduced in those with a history of active tuberculosis. No association was seen between a history of active tuberculosis and FEV1/FVC.

A history of active tuberculosis was associated with self-reported respiratory symptoms at Visit 2: cough (OR [95%CI]) (1.43 [1.10, 1.87];  $p=0.008$ ) and production of phlegm when coughing (1.64 [1.21, 2.22];  $p=0.001$ ) (Table 5). A history of active tuberculosis was not significantly associated with frequent cough (4-6x/day), stopping for breath while walking, or shortness of breath when hurrying on the level or walking up a slight hill.

We found no effect modification for the association of prior active tuberculosis with airflow obstruction or spirometric restriction by sex, age, diabetes, or BMI (Figure 1). By smoking status, effect modification was significant for a spirometric restrictive pattern (P-interaction=0.04) with the association being markedly stronger among former smokers (OR [95%CI]) (3.01 [1.77, 5.13]).

#### *Additional analysis of arsenic and tuberculosis*

For airflow obstruction and spirometric restrictive pattern, the association with prior active tuberculosis became slightly stronger when models were additionally adjusted for arsenic when using the fixed-ratio (obstruction: 1.47 [1.07, 2.02]) (restriction: 1.90 [1.34, 2.70]) (Table 3, model 4). When using the LLN, results remained non-significant.

By arsenic exposure tertile, effect modification was statistically significant for the spirometric restrictive pattern (P-interaction=0.03) with stronger odds ratios for those in arsenic tertile 2 (2.70 [1.44, 5.10]) and tertile 3 (2.63 [1.39, 4.99]) compared to tertile 1 (1.17 [0.60, 2.28]) (Figure 1). No interaction was observed between arsenic and prior active tuberculosis for obstruction (P-interaction=0.2), although a stronger association between prior active tuberculosis and obstruction was observed among those in the highest arsenic tertile (2.27 [1.28, 4.05]).

For FEV1 % predicted, the mean difference (95%CI) comparing those with and without a history of active tuberculosis was further reduced with each increasing arsenic exposure tertile, with the largest reduction in those highest exposed (-3.32 [-7.02, 0.39])%,

-5.97 [-9.91, -2.04]%, -8.86 [-13.08, -4.64]% for tertiles 1, 2 and 3 respectively) (Figure 2). The same pattern was seen for FVC % predicted (-3.93 [-7.19, -0.66]%, -6.27 [-10.36, -2.19]%, -6.48 [-10.64, -2.32]%, respectively). However, the interaction was not statistically significant for either FEV1 % predicted or FVC % predicted.

Arsenic exposure was significantly associated with a reduced odds of a past active tuberculosis diagnosis (Table 6). In fully adjusted models, the odds ratio [95% CI] comparing the highest to lowest arsenic tertile ( $\geq 12.0$  vs.  $\leq 6.0$   $\mu\text{g/g}$  creatinine) was 0.71 [0.56, 0.89].

## DISCUSSION

From our findings, lung function and respiratory symptoms cough and cough with phlegm appear worse in participants who had a history of active tuberculosis compared to those who did not. A history of active tuberculosis was associated with reduced FEV1 % predicted and FVC % predicted and increased odds of airflow obstruction and a spirometric restrictive pattern, with a stronger association with the restrictive pattern, when based on the fixed-ratio definition. The associations were significant after adjustment for diabetes and major risk factors, including smoking. While the interaction analysis was underpowered and none of the p-values reached significance, the effect estimates showed lower FEV1 % predicted and lower FVC % predicted with preserved FEV1/FVC ratio comparing tuberculosis to no tuberculosis among those with arsenic levels in highest ( $>12.0$   $\mu\text{g/L}$ ) compared to lowest tertile ( $\leq 6.0$   $\mu\text{g/L}$ ).

Our findings support existing knowledge that a history of active tuberculosis is a risk factor for long-term respiratory impairment.<sup>4</sup> An increasing number of population-based studies have shown a consistent positive association between a history of active tuberculosis and the presence of airflow obstruction, with a recent meta-analysis finding a history of active tuberculosis to be associated with chronic obstructive pulmonary disease in adults over 40 years of age (pooled odds ratio 3.05 [242, 3.85]).<sup>21</sup> A study of 14,050 adults from 18 countries found that a history of self-reported tuberculosis increased risk for airflow obstruction (adjusted odds ratio 2.51 [1.83, 3.42] using the LLN definition).<sup>22</sup> The study also found an association with spirometric restriction (2.13 [1.42, 3.19]). In our study, the associations with the study outcomes based on the LLN were not statistically significant, possibly because of the smaller number of cases and a lack of power. The Global Initiative for Obstructive Lung Disease (GOLD) threshold of  $<0.70$  for FEV1/FVC is thought to often misclassify normal spirometry as airflow obstruction in non-smokers, particularly in older adults.<sup>23</sup> The American Thoracic Society recommends using the LLN instead of the fixed GOLD ratio. However, it is likely that the LLN misses individuals with mild airflow obstruction.<sup>24</sup> In a population with a high burden of lung disease, as it appears to be in the SHS, underdiagnosis of obstruction may be a larger problem than overdiagnosis.<sup>25</sup> Overall, however, why the associations are stronger with the ratio vs. LLN definition is unclear.

Fewer studies have examined post-tuberculosis respiratory health in an indigenous population, with none in an American Indian population. One descriptive study (N=121) examined respiratory health post-tuberculosis, comparing indigenous to

non-indigenous people from Brazil, and found a high prevalence of respiratory symptoms, obstruction, and obstruction with reduced FVC in both groups.<sup>26</sup>

It is proposed that the chronic inflammatory response and long-term anatomic alterations induced by pulmonary tuberculosis are the main pathological basis for long-term impairment of lung function.<sup>27</sup> A number of mechanisms may account for the development of airflow obstruction after pulmonary tuberculosis infection, including the structural damage of large and small airways including bronchiolar narrowing and bronchiolitis obliterans resulting from peribronchial fibrosis as well as accelerated emphysematous change caused by residual chronic or recurrent inflammation.<sup>28, 29</sup>

Restriction in tuberculosis patients may be explained by structural changes in the lung as a result from aberrant lung tissue repair, such as bronchovascular distortion, fibrotic bands, and pleural thickening.<sup>4</sup> There also could be significant overlap of obstruction and restrictive impairment mechanisms in those with tuberculosis, with some researchers suggesting that immune mediators and pathways that drive caseous necrosis and pulmonary cavitation, which can lead to airflow obstruction, during the disease may also set up for later fibrosis.<sup>4</sup> Rather than a direct toxic effect of arsenic on the lung, an inflammation-mediated immunologic basis has been suggested,<sup>30</sup> as arsenic is known to alter key functions of the innate and adaptive immune system.<sup>31-34</sup> In mice, exposure of low to moderate concentrations of arsenic in drinking water (10 – 100 µg/L) led to a decrease in immune gene expression and aberration in inflammatory protein expression,<sup>9, 35</sup> resulting in susceptibility to airway inflammation.<sup>10</sup> Both arsenic<sup>36, 37</sup> and tuberculosis<sup>21</sup> are known to be associated with increased risk of developing bronchiectasis, suggesting some potential common pathophysiology for the long-term impact of arsenic and

tuberculosis on lung disease. In both tuberculosis-associated lung injury and arsenic-induced effects on airway physiology, matrix metalloproteinases (MMPs), degradation enzymes, are likely central; MMPs can promote different stages of lung remodeling during tuberculosis including promoting alveolar destruction<sup>38</sup> and, in arsenic-exposed individuals, MMP-9 impairs repair mechanisms in human lung epithelial cells.<sup>39</sup>

In the additional analysis, the effect estimates for the association between history of tuberculosis and lung function indices FEV1 % predicted and FVC % predicted were progressively decreased by increasing urinary arsenic concentrations, however the p-values for interaction were not statistically significant. Despite this dose-response, elevated arsenic exposure was unexpectedly associated with reduced odds of a history of active tuberculosis. This is inconsistent with the one previous study also examining this relationship, an ecological study from Chile, which found increased mortality from pulmonary tuberculosis associated with arsenic in drinking water.<sup>8</sup> We hypothesize that our findings may be due to survival bias. For example, those with more severe tuberculosis may have died prior to participation in the SHS. It is also possible those with higher arsenic exposure were more likely to progress from latent to active tuberculosis, or, at the time of active tuberculosis development, also had higher risk of death. We were not able to determine if arsenic could have increased the incidence of active tuberculosis or increased mortality among infected individuals. Relevant to this population, older age, diabetes, and chronic obstructive pulmonary disease have been associated with an increased risk of death during tuberculosis treatment.<sup>40</sup> In these scenarios, our sample of tuberculosis patients could be over-representing those with better survival after treatment, including participants with lower arsenic exposure. This could have attenuated

effect estimates, undervaluing the relationship between tuberculosis and arsenic exposure. Additionally, if the most severely affected tuberculosis patients were not included in the study, all effect estimates shown, including the main analyses and possible interaction with arsenic, could be underestimated.

Being able to run analyses for both active tuberculosis and a positive tuberculosis diagnostic test (suggestive of latent tuberculosis) could have provided additional clarity into the relationship with lung health and with arsenic, potentially to help determine if there was an increased risk of tuberculosis activation in those with both latent tuberculosis and higher arsenic exposure. This could help us assess arsenic's contribution to pulmonary impairment through tuberculosis activation. A commonality among the majority of risk factors for tuberculosis activation, like HIV and malnutrition, is an impaired immune response.<sup>41</sup> Part of the toxic effects of arsenic is likely through acting as an immunosuppressant<sup>42</sup> and producing a state which favors opportunistic infections,<sup>43</sup> like tuberculosis. Animal studies have demonstrated immune suppression that is suspected to affect the pulmonary defense system,<sup>44</sup> and studies in children have shown associations between increased urinary arsenic and reduced proliferative response to mitogens, percentage of CD4 T cells and IL-2 secretion levels, suggesting immunosuppression.<sup>45</sup> Our analyses are based on a clinical diagnosis of active tuberculosis and not the tuberculin skin test, the purified protein derivative (PPD) test, the available screening test at the time of the study visit. This is because the administration of the Bacille Calmette-Guerin (BCG) vaccine could have interfered with the interpretation of the PPD test, as those who have received the vaccination also test positive for the PPD skin test. The study population was part of a large BCG vaccination trial during 1935-



1938, during which children and adults aged 1 month to 20 years who had normal chest radiographs received the BCG vaccine or placebo, with a considerable degree of protection found throughout the 60 years of follow-up;<sup>46</sup> we did not have individual records of vaccination status.

This study benefitted from several strengths. The SHS is a well-established cohort with high-quality laboratory methods, high participation retentions, standardized variable collection, and strong support from the communities involved. We had individual spirometric measures standardized to American Thoracic Society recommendations. We also had American Indian reference values derived from the SHS population, which allowed us to assess lung function against predicted values for better interpretation of results. However, the subgroup used to calculate predicted values did not exclude those with tuberculosis or high arsenic exposure.

Our study has several limitations. Outcome misclassification could have occurred from inaccurate recall of symptom and use of symptom questionnaires based on yes/no answers, which might be difficult for participants to choose from compared to scale-based questionnaires. Determination of prior active tuberculosis infection was dependent on the completeness and accuracy of medical records. If any information pertaining to tuberculosis was inadequately documented, it would have been missed in our analysis; however, as diagnosis of tuberculosis among American Indians has long been a major concern, misdiagnosis is thought unlikely.<sup>46</sup> More importantly, even if some cases were missed, diagnosis based on laboratory test and the combination of a radiological criteria with tuberculosis treatment ensure the high specificity of the case definition. Although

we did not have confirmation whether the active tuberculosis was pulmonary or extra pulmonary, around 80% of active tuberculosis cases in American Indians in the United States are pulmonary;<sup>47</sup> however this could have led to an underestimation of effect estimates for pulmonary tuberculosis, as the number of cases was likely slightly diluted by extrapulmonary cases. While we had no information on HIV infection, the strongest known risk factor for progressing latent tuberculosis infection to tuberculosis disease, the HIV infection among American Indian patients with active tuberculosis is comparatively low than for other racial/ethnic groups.<sup>47</sup> Our study is cross-sectional and precludes us from drawing temporal conclusions. The diagnosis of active tuberculosis happened in the past and was based on medical records; we do not know when airflow obstruction or spirometric restriction developed and we cannot discount the possibility they were present prior to tuberculosis. Additionally, due to incomplete data collection for year of tuberculosis diagnosis, we were not able to use it with confidence in our analyses, further preventing us from examining temporality. We did not account for multiple comparisons, because while we examined two exposures (arsenic and tuberculosis) individually with each outcome, we were not interpreting the results separately. Rather, the multiple outcomes were not independent and provided complementary information as we examined several ways to assess the pattern of lung impairment (obstructive vs. restrictive), looking for patterns of associations with the study outcomes that allowed us to assess the contribution of tuberculosis and joint effect with arsenic. We lacked information on possible additional confounders, such as exposure to indoor air pollutants, including exposure to smoke from cooking fires or heating fuel, and dietary information, including consumption levels of marine fatty acids and fresh fruit and vegetables.<sup>48</sup>

Regarding socioeconomic status, we used education status which is a proxy commonly used by the SHS, but that might not completely capture study participants' socioeconomic status.

## **CONCLUSIONS**

A prior active tuberculosis diagnosis was associated with impaired pulmonary function, including airflow obstruction and a spirometric restrictive pattern, and respiratory symptoms among American Indians in the Strong Heart Study, a population historically at elevated risk for tuberculosis infection and disease. We also found suggestive evidence of a possible interaction between arsenic exposure and a history of active tuberculosis with worse lung function, especially spirometric restrictive-related outcomes. The possible interaction between arsenic and active tuberculosis, as well as the reduced odds of active tuberculosis associated with arsenic exposure, warrants further investigation, as many populations at risk of developing tuberculosis are also exposed to arsenic-contaminated water.

## TABLES

**Table 1. Participant characteristics by cumulative prevalence of history of medical-record tuberculosis (N=2,463)**

	No tuberculosis (n=2,119)	Tuberculosis (n=344)
Age, years	58.5 (53.0 – 65.3)	60.8 (55.5 – 66.8)
Female	1,274 (60.1%)	226 (65.7%)
Education		
No high school (HS)	356 (16.8%)	67 (19.5%)
Some HS	491 (23.2%)	97 (28.2%)
Completed HS or higher	1,271 (60.0%)	180 (52.2%)
BMI, kg/m <sup>2</sup>	30.1 (26.8 – 34.4)	30.0 (26.5 – 33.8)
Waist circumference (cm)	105 (96 – 114)	104 (95 – 114)
% Body fat	36.1 (29.3 – 43.0)	37.1 (30.1 – 42.5)
Diabetes	1,091 (51.5%)	187 (54.4%)
Urine $\Sigma$ As*	8.5 (5.1 – 14.0)	7.6 (5.0 – 12.9)
%iAs	7.5 (5.4 – 10.8)	7.6 (5.4 – 10.7)
%MMA	14.1 (10.9 – 17.6)	14.2 (11.1 – 18.2)
%DMA	77.9 (71.9 – 82.8)	77.8 (71.7 – 82.9)
Smoking status		
Never	640 (30.2%)	100 (29.1%)
Former	741 (35.0%)	115 (33.4%)
Current	738 (34.8%)	129 (37.5%)
Cigarette pack years	3 (0 – 18)	3 (0 – 16.5)
FEV1, mL	2.5 (2.1 – 3.0)	2.3 (1.8 – 2.8)
FVC, mL	3.3 (2.7 – 4.0)	3.0 (2.4 – 3.8)
FEV1:FVC ratio, %	76.7 (71.5 – 80.1)	75.6 (69.0 – 80.6)
% Predicted		
FEV1	94.1 (82.2 – 104.8)	88.5 (75.5 – 100.7)
FVC	94.4 (83.3 – 105.3)	91.1 (78.3 – 100.7)
Airflow obstruction (fixed)	427 (20.2%)	94 (27.3%)
Airflow obstruction (LLN)	141 (6.7%)	33 (9.6%)
Restrictive pattern (fixed)	305 (14.4%)	64 (18.6%)
Restrictive pattern (LLN)	148 (7.0%)	30 (8.7%)
Self-reported cough	451 (21.3%)	98 (28.5%)
Cough 4-6x/week	286 (13.5%)	59 (17.2%)
Phlegm with cough	276 (13.1%)	70 (20.4%)
Shortness of breath	959 (45.8%)	171 (50.3%)
Stopping for breath	332 (15.9%)	75 (22.1%)

Data are median (interquartile range) or n (% of column)

\* $\mu$ g/g creatinine;  $\Sigma$ As = inorganic arsenic plus methylated species

\*\*For continuous variables, ANOVA was used to calculate p-value; for categorical variables, chi-square test was used

**Table 2. Participant characteristics by airflow obstruction and spirometric restrictive pattern (N=2,463)**

	<b>Airflow obstruction</b> FEV1/FVC <0.70 (n=521)	<b>Restrictive pattern</b> FEV1/FVC >0.70 FVC <80% predicted (n=369)	<b>Control</b> FEV1/FVC >0.70 FVC >80% predicted (n=1,573)
Age, years	63.5 (56.7 – 69.7)	59.8 (54.1 – 65.7)	57.2 (52.3 – 63.8)
Female	256 (50.9%)	246 (66.7%)	998 (63.5%)
Education			
No high school (HS)	134 (25.7%)	80 (21.7%)	209 (13.3%)
Some HS	132 (25.3%)	94 (25.5%)	362 (23.0%)
Completed HS or higher	255 (48.9%)	194 (52.7%)	1,002 (63.7%)
Smoking status			
Never	122 (23.4%)	121 (32.8%)	491 (31.6%)
Former	170 (32.6%)	131 (35.5%)	555 (35.3%)
Current	229 (44.0%)	117 (31.7%)	521 (33.1%)
Smoking pack years	9.0 (0 – 33.0)	3.0 (0 – 15.0)	2.0 (0 – 14.0)
BMI, kg/m <sup>2</sup>	28.1 (25.0 – 31.9)	31.6 (27.9 – 36.3)	30.5 (27.3 – 34.4)
Diabetes	231 (44.3%)	251 (68.0%)	796 (50.6%)
Urine $\Sigma$ As, $\mu$ g/g creatinine*	10.1 (5.7 – 14.6)	9.1 (5.1 – 16.2)	7.8 (4.9 – 13.0)
FEV1, %predicted	79.9 (63.9 – 93.8)	75.2 (69.3 – 80.8)	99.2 (91.8 – 108.5)
FVC, %predicted	95.5 (79.2 – 108.6)	72.0 (65.7 – 76.9)	97.4 (89.7 – 106.3)
FEV1/FVC, %	65.2 (58.7 – 68.1)	80.5 (76.3 – 85.3)	77.9 (74.8 – 81.3)
Self-reported symptoms			
Cough	155 (29.8%)	101 (27.5%)	293 (18.7%)
Cough 4-6x/week	105 (20.2%)	63 (17.2%)	177 (11.3%)
Phlegm with cough	101 (19.4%)	60 (16.4%)	185 (11.8%)
Shortness of breath	255 (49.4%)	197 (55.0%)	678 (43.5%)
Stopping for breath	113 (21.9%)	80 (22.5%)	214 (13.8%)
History of active tuberculosis	94 (18.0%)	64 (17.3%)	186 (11.8%)

All analyses are weighted. Data are n (% of column), or median (interquartile range)

\* $\mu$ g/g creatinine;  $\Sigma$ As = inorganic arsenic plus methylated species; arsenic measured from Visit 1 (1989-1991)

**Table 3. Odds ratio (95% confidence interval) of airflow obstruction and spirometric restrictive pattern by history of active tuberculosis**

	No tuberculosis	Tuberculosis	P-value
<b>Obstruction<sup>†</sup> Fixed-ratio/ Control<sup>Ω</sup></b>	427/1,387	94/186	
Model 1	1.00 (Ref)	1.43 (1.07, 1.91)	0.02
Model 2	1.00 (Ref)	1.47 (1.09, 1.97)	0.01
Model 3	1.00 (Ref)	1.45 (1.08, 1.95)	0.01
Model 4	1.00 (Ref)	1.47 (1.07, 2.02)	0.02
<b>Obstruction<sup>†</sup> Lower limit of normal/ Control<sup>Ω</sup></b>	141/1,830	33/281	
Model 1	1.00 (Ref)	1.28 (0.85, 1.92)	0.24
Model 2	1.00 (Ref)	1.28 (0.84, 1.94)	0.25
Model 3	1.00 (Ref)	1.24 (0.81, 1.89)	0.33
Model 4	1.00 (Ref)	1.27 (0.80, 2.00)	0.31
<b>Restrictive<sup>a</sup> Fixed-ratio/ Control<sup>Ω</sup></b>	305/1,387	64/186	
Model 1	1.00 (Ref)	1.72 (1.25, 2.37)	0.001
Model 2	1.00 (Ref)	1.73 (1.25, 2.39)	0.001
Model 3	1.00 (Ref)	1.73 (1.24, 2.40)	0.001
Model 4	1.00 (Ref)	1.90 (1.34, 2.70)	<0.001
<b>Restrictive<sup>a</sup> Lower limit of normal/ Control<sup>Ω</sup></b>	148/1,830	30/281	
Model 1	1.00 (Ref)	1.53 (1.00, 2.34)	0.05
Model 2	1.00 (Ref)	1.52 (0.99, 2.33)	0.05
Model 3	1.00 (Ref)	1.47 (0.97, 2.29)	0.07
Model 4	1.00 (Ref)	1.38 (0.86, 2.22)	0.19

<sup>†</sup> Fixed airflow obstruction:

Fixed-ratio: FEV1/FVC <0.70

Lower limit of normal: FEV1/FVC <LLN

<sup>a</sup> Restrictive pattern:

Fixed-ratio: FEV1/FVC >0.70 & FVC <80% predicted

Lower limit of normal: FEV1/FVC >LLN & FVC <LLN

<sup>Ω</sup> Control:

Fixed-ratio: FEV1/FVC >0.70 & FVC >80% predicted

Lower limit of normal: FEV1/FVC >LLN and FVC >LLN

Model 1: adjusted for age, sex, education, site

Model 2: further adjusted for smoking status and smoking pack-year

Model 3: further adjusted for BMI, waist circumference, percent body fat, diabetes

Model 4: further adjusted for arsenic

**Table 4. Mean difference (95% Confidence Interval) of lung function measures comparing participants with vs. without history of active tuberculosis**

	N	Mean difference (95%CI)	P-value
<b>FEV1, % predicted</b>			
All	2,462	-5.84 (-7.91, -3.77)	<0.001
Healthy <sup>a</sup>	1,573	-2.73 (-4.64, -0.83)	0.005
<b>FVC, % predicted</b>			
All	2,462	-5.23 (-7.45, -3.39)	<0.001
Healthy <sup>a</sup>	1,573	-2.70 (-4.51, -0.89)	0.004
<b>FEV1/FVC ratio (%)</b>			
All	2,462	-0.43 (-1.40, 0.54)	0.38
Healthy <sup>a</sup>	1,573	-0.04 (-0.71, 0.64)	0.92

<sup>a</sup> Healthy: FEV1/FVC >0.70 & FVC >80% predicted

Adjusted for: age, sex, education, site, smoking status, cigarette pack-year, BMI, waist circumference, % body fat, and diabetes

**Table 5. Odds ratio (95% Confidence Interval) of self-reported respiratory symptom by history of active tuberculosis**

	No tuberculosis	Tuberculosis	P-value
<b>Cough/No cough*</b>	451/1,663	98/246	
Model 1	1.00 (Ref)	1.41 (1.09, 1.83)	0.01
Model 2	1.00 (Ref)	1.44 (1.10, 1.88)	0.007
Model 3	1.00 (Ref)	1.44 (1.11, 1.88)	0.007
Model 4	1.00 (Ref)	1.43 (1.10, 1.87)	0.008
Model 5	1.00 (Ref)	1.34 (1.01, 1.79)	0.04
<b>Cough 4-6x per day<sup>Δ</sup>/No</b>	286/1,826	59/285	
Model 1	1.00 (Ref)	1.29 (0.94, 1.76)	0.11
Model 2	1.00 (Ref)	1.31 (0.95, 1.80)	0.10
Model 3	1.00 (Ref)	1.32 (0.96, 1.82)	0.09
Model 4	1.00 (Ref)	1.31 (0.95, 1.81)	0.10
Model 5	1.00 (Ref)	1.22 (0.86, 1.71)	0.26
<b>Phlegm/No phlegm<sup>†</sup></b>	276/1,836	70/274	
Model 1	1.00 (Ref)	1.59 (1.19, 2.14)	0.002
Model 2	1.00 (Ref)	1.63 (1.21, 2.21)	0.001
Model 3	1.00 (Ref)	1.65 (1.22, 2.23)	0.001
Model 4	1.00 (Ref)	1.64 (1.21, 2.22)	0.001
Model 5	1.00 (Ref)	1.53 (1.10, 2.11)	0.01
<b>Shortness of breath/No<sup>‡</sup></b>	959/1,134	171/169	
Model 1	1.00 (Ref)	1.08 (0.86, 1.37)	0.50
Model 2	1.00 (Ref)	1.09 (0.86, 1.39)	0.46
Model 3	1.00 (Ref)	1.12 (0.88, 1.43)	0.35
Model 4	1.00 (Ref)	1.12 (0.88, 1.43)	0.36
Model 5	1.00 (Ref)	1.13 (0.87, 1.46)	0.37
<b>Stop for breath/No<sup>§</sup></b>	332/1,756	75/264	
Model 1	1.00 (Ref)	1.28 (0.95, 1.72)	0.10
Model 2	1.00 (Ref)	1.30 (0.97, 1.75)	0.08
Model 3	1.00 (Ref)	1.34 (0.99, 1.80)	0.05
Model 4	1.00 (Ref)	1.33 (0.99, 1.80)	0.06
Model 5	1.00 (Ref)	1.35 (0.98, 1.86)	0.07

Model 1: adjusted for age, sex, education, site

Model 2: further adjusted for smoking status and smoking pack-year

Model 3: further adjusted for BMI, waist circumference, percent body fat

Model 4: further adjusted for diabetes

Model 5: further adjusted for arsenic

\*\*Do you usually have a cough?

<sup>Δ</sup>Do you usually cough as much as 4-6 times/day, 4 or more days/week?

<sup>†</sup>Do you usually bring up phlegm when you cough?

<sup>‡</sup>Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?

<sup>§</sup>Do you ever have to stop for breath while walking about 100 yards or a few minutes on the level?



**Table 6. Odds ratio (95% Confidence Interval) of history of tuberculosis by urinary arsenic concentration\***

	Inorganic Plus Methylated Arsenic Species $\mu\text{g/g}$ creatinine			75 <sup>th</sup> vs. 25 <sup>th</sup> Percentile <sup>‡</sup>	P-trend**
	Tertile 1 $\leq 6.0^*$	Tertile 2 6.1-11.9*	Tertile 3 $\geq 12.0^*$		
<b>History of Tuberculosis/ No tuberculosis</b>	111/606	100/625	88/608	299/1,839	
Model 1	1.00 (Ref)	0.71 (0.52, 0.97)	0.61 (0.43, 0.88)	0.74 (0.59, 0.92)	0.007
Model 2	1.00 (Ref)	0.71 (0.52, 0.97)	0.61 (0.43, 0.87)	0.73 (0.59, 0.91)	0.006
Model 3	1.00 (Ref)	0.71 (0.52, 0.96)	0.59 (0.41, 0.85)	0.72 (0.57, 0.90)	0.004
Model 4	1.00 (Ref)	0.70 (0.51, 0.96)	0.58 (0.41, 0.84)	0.71 (0.56, 0.89)	0.003

\*Tertiles are range; calculated based on overall population; sum of iAs, MMA, DMA  $\mu\text{g/g}$  creatinine

\*\*P-trend calculated modeling log-arsenic as continuous

<sup>‡</sup> Comparison of the 75<sup>th</sup> and 25<sup>th</sup> percentiles (interquartile range) of urinary arsenic concentrations (14.3 vs. 5.1  $\mu\text{g/g}$  creatinine)

Model 1: adjusted for age, sex, education, site

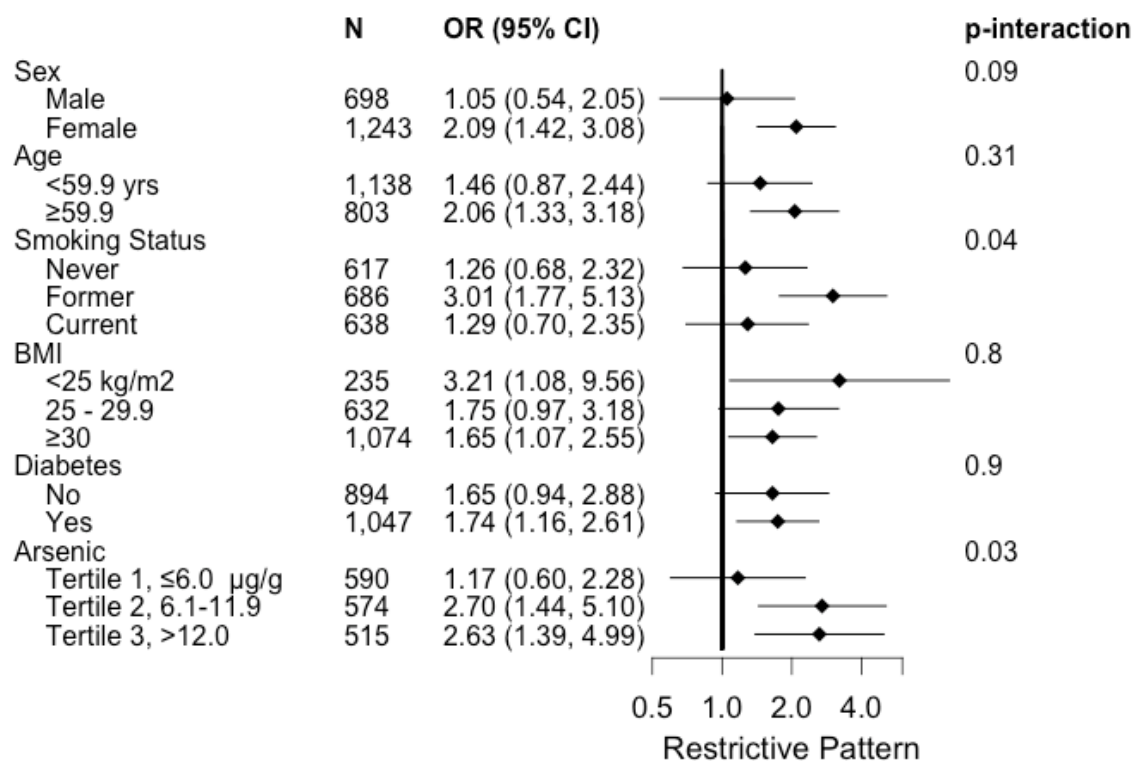
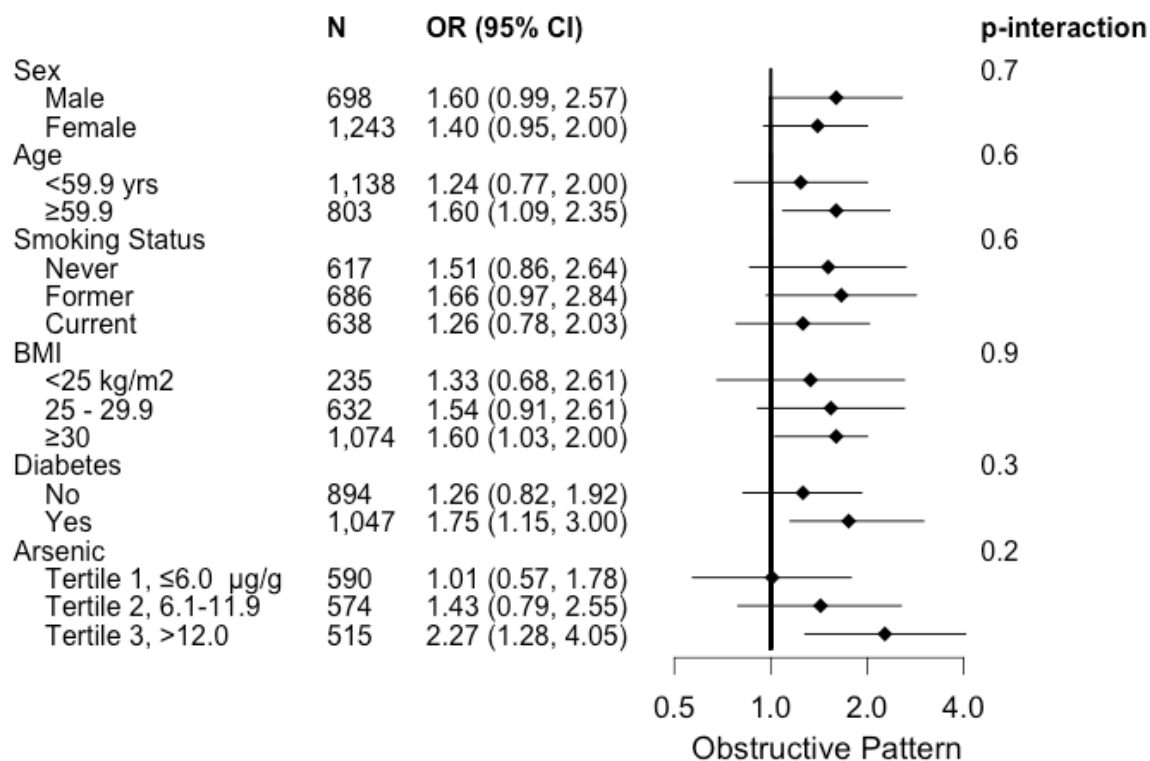
Model 2: further adjusted for smoking status and smoking pack-year

Model 3: further adjusted for BMI, waist circumference, percent body fat

Model 4: further adjusted for diabetes

## FIGURES

**Figure 1. Odds ratio (95% confidence interval) for airflow obstruction and restrictive pattern (fixed-ratio) when history of tuberculosis is compared across participant characteristics**

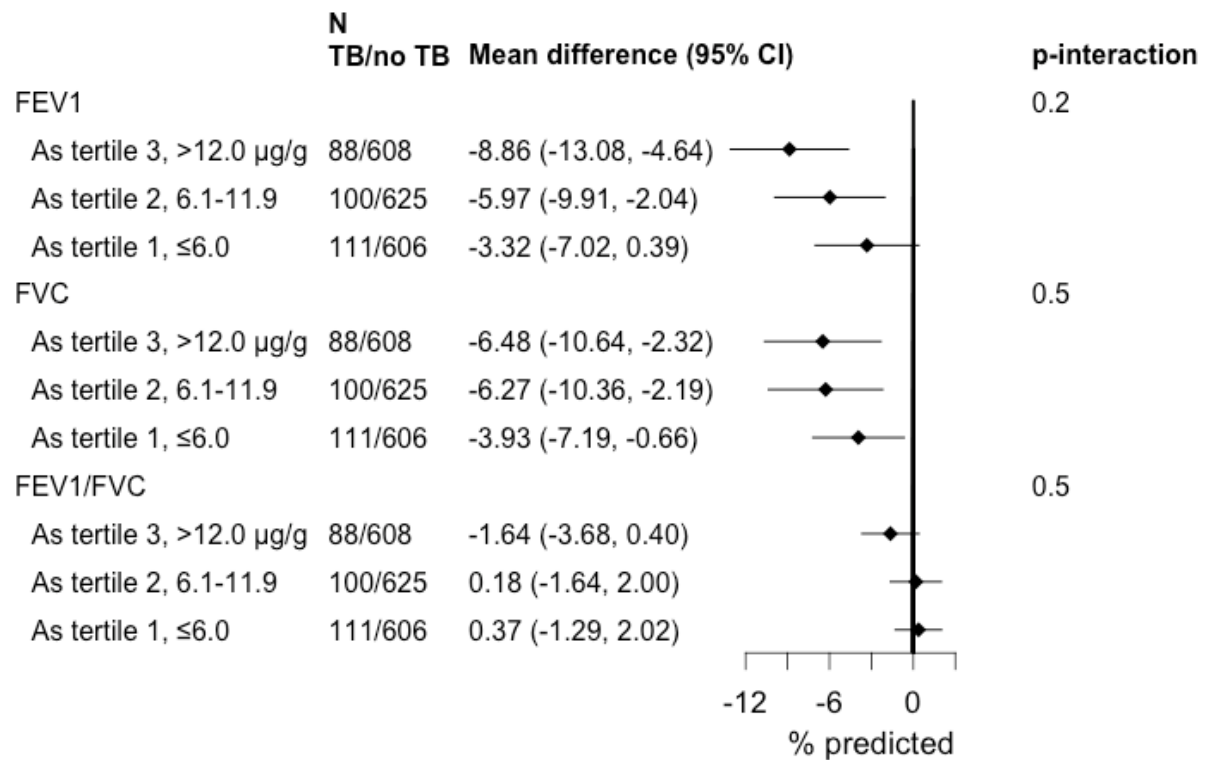


\*ORs were stratified by each subgroup of interest, and associated *P* values for interaction were obtained from models with interaction terms and using Wald tests for multiple coefficients

Age= mean

Adjusted for: age, sex, education, location, smoking status, cigarette pack-year, BMI, waist circumference, % body fat, and diabetes.

**Figure 2. Mean difference (95% confidence interval) of lung function (FEV1, FVC percent predicted) by tuberculosis and urine arsenic tertile**



Adjusted for: age, sex, education, location, smoking status, cigarette pack-year, BMI, waist circumference, % body fat, and diabetes.

### CHAPTER 3

Arsenic in Groundwater in Private Wells in Rural North Dakota and South Dakota:  
*Water Quality Assessment for an Intervention Trial*

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## ABSTRACT

Elevated exposure to arsenic disproportionately affects populations relying on private well water in the United States (US). This includes many American Indian (AI) communities where naturally occurring arsenic is often above 10 µg/L, the current US Environmental Protection Agency safety standard. The Strong Heart Water Study is a randomized controlled trial aiming to reduce arsenic exposure to private well water users in AI communities in North Dakota and South Dakota. In preparation for this intervention, 371 households were included in a community water arsenic testing program to identify households with arsenic  $\geq 10$  µg/L by inductively coupled plasma mass spectrometry (ICP-MS). Arsenic  $\geq 10$  µg/L was found in 97/371 (26.1%) households; median water arsenic concentration was 6.3 µg/L, ranging from  $<1$  to 198 µg/L. Silica was identified as a water quality parameter that could impact the efficacy of arsenic removal devices to be installed. A low-range field rapid arsenic testing kit evaluated in a small number of households was found to have low accuracy; therefore, not an option for the screening of affected households in this setting. In a pilot study of the effectiveness of a point-of-use adsorptive media water filtration device for arsenic removal, all devices installed removed arsenic below 1 µg/L at both installation and 9 months post-installation. This study identified a relatively high burden of arsenic in AI study communities as well as an effective water filtration device to reduce arsenic in these communities. The long-term efficacy of a community-based arsenic mitigation program in reducing arsenic exposure and preventing arsenic related disease is being tested as part of the Strong Heart Water Study.

## INTRODUCTION

In the United States, the estimated population using domestic wells for drinking water with arsenic (As) levels above the Environmental Protection Agency (EPA) maximum contaminant level (MCL) of 10 µg/L is 2.1 million people <sup>1</sup>, with an additional 384,000 people exposed through public water systems <sup>2</sup>. Arsenic is a highly toxic and carcinogenic element, classified by the US Agency for Toxic Substances and Disease Registry as the top substance on its priority list of hazardous substances <sup>3</sup>. Millions more are exposed to arsenic in drinking water below the MCL, which is of concern as the evidence suggests no safe threshold exists <sup>4</sup>. Increasing evidence supports the role of low-moderate arsenic (<50 µg/L) in cancer and cardiovascular disease, and potentially diabetes, neurodevelopmental toxicity, immune effects and nonmalignant respiratory disease <sup>5</sup>.

Private wells do not fall under the jurisdiction of the EPA's Safe Drinking Water Act, and it is the responsibility of the well owner to make sure their water is safe. Major barriers to arsenic water testing include general awareness, geographic distance to a laboratory and lack of access to water testing <sup>6</sup>, and the high price point per test (~20 USD per sample) <sup>7-9</sup>. Rural and suburban families relying on ground water, including many in American Indian (AI) communities, are the most affected, especially in the Southwest, Midwest and Northeast US <sup>10</sup>. The concentration of naturally occurring arsenic in ground water varies regionally due to a combination of climate and geology, with greater concentrations found in certain areas of the US including the Interior Plains. <sup>11</sup> In AIs who participated in the Strong Heart Study (SHS), an ongoing cohort study of cardiovascular disease and its risk factors among AIs, arsenic has been

associated with an increased risk of cardiovascular disease, diabetes, kidney disease, and some cancers <sup>12-14</sup>, highlighting the urgency of preventing arsenic exposure for those relying on private wells.

The Strong Heart Water Study (SHWS), the first randomized controlled trial of an arsenic intervention in the US, was developed to reduce arsenic exposure in AI communities in North Dakota and South Dakota. High arsenic in ground water in aquifers composed of felsic volcanic rocks is found in these areas.<sup>11</sup> All participating households receive a point-of-use filter to remove arsenic from drinking and cooking water and are randomly assigned to receive an intensive health promotion program or the standard program. In preparation for the intervention, a water quality assessment was performed between February 2014 and January 2018 to achieve the following objectives: (1) to identify households with private wells with elevated arsenic that are eligible for the SHWS using inductive coupled plasma mass spectrometry (ICP-MS); (2) to assess water quality parameters that could interfere with the efficacy of the point-of-use adsorptive media filter and (sub-objective 1) to evaluate the accuracy of the Arsenic Econo-Quick™ (Industrial Test Systems, Inc.) test as a potential rapid screening tool for eligible households; and (3) to evaluate the efficacy of the selected point-of-use adsorptive media filter in study households.

## **METHODS**

### **Study Area and Private Well Testing**

The study area consists of households using private wells for drinking water in three Tribal Nations in South Dakota and North Dakota, communities referred to as A, B,



and C (as requested by the communities which prefer their names are not made public). Convenience sampling was performed by study team members to test domestic wells from 2014 to 2018 (N=371). Strategies used to identify those homes included word of mouth, health fairs, radio, community member contacts, and a database of previously tested wells. In November 2015, a more detailed water quality assessment was performed in 29 households, chosen by convenience sampling and willingness to participate. Of those 29 households, 19 had also been tested for arsenic in February/March 2014, allowing the examination of arsenic temporality in the study area.

### **Water Sample Collection**

Water samples were collected from the kitchen faucet using a sampling and analysis plan developed from EPA guidelines <sup>15</sup>. Water sampling locations were determined by a handheld GPS (Global Positioning System) navigator (Garmin eTrex 10). Water samples for ICP-MS arsenic testing (Objective 1) were collected in 20 mL scintillation vials. Duplicate samples were collected from each well, however only one sample has been analyzed from each well to date. For detailed water quality analyses (Objective 2), acid-washed 125mL plastic bottles were used to collect filtered samples for iron and phosphorus testing; non-acid-washed bottles to collect samples for alkalinity, sulfate, and silica; a non-acid-washed bottle to collect filtered samples for nitrate; a 20 mL scintillation vial to collect samples for arsenic, uranium, lead, and cadmium for ICP-MS analysis; arsenic speciation filters to collect samples for ICP-MS As(III) analysis; and a multi-parameter water quality sonde (YSI Inc./Xylem Inc.) to test for pH. To test a rapid water arsenic screening kit (Objective 3), water samples were collected in an acid-

washed plastic beaker and then poured into reaction bottles (clear PVC) supplied in the arsenic testing kits.

**Objective 1: ICP-MS Testing of 342 Households in the Study Area for Arsenic  $\geq 10$   $\mu\text{g/L}$  (2014-2018)**

Water samples (n= 342) were transported to Mid Continent Testing Labs, Inc. (Rapid City, South Dakota) for ICP-MS arsenic analysis. The number of samples tested by Mid Continent per community was 319, 15, and 8 in communities A, B and C, respectively from 2014 to 2018. The larger number of samples in Community A is related to more extensive sampling in Community A, which is the focus of the SHWS intervention. The quality assurance program employed by the laboratory has a variety of checks to ensure accuracy of results. Prior to each day's use, the ICP-MS was run through an optimization and mass calibration, selecting the optimum instrument parameters for the day. The instrument was calibrated by testing various standards, in the case of arsenic analysis, using 2, 5, 10, 20, and 100 ppb standard solutions. The calibration was then checked on two 50 ppb stock solutions. The first is the Initial Calibration Verification (ICV), prepared from a different source from the calibration standards. The second is the Continuing Calibration Verification (CCV), prepared from the same source as the calibration standards. Both must show a value of 50 ppb, within  $\pm 10\%$  of expected value. The CCV was checked at least every 10 samples tested throughout the day. A blank DI solution was also checked, the Initial Calibration Blank (ICB). Mid Continent also uses a Matrix Spike and a Matrix Spike Duplicate to ensure accuracy. At least every 10 samples, a small concentration of arsenic, 25 ppb, was added

to two aliquots of the sample, and should get 90-110% recovery from the spiked samples. For any samples that are digested, the lab also carries a Blank and Fortified Blank through the process to demonstrate proper recovery and lack of sample contamination through digestion. During all calibration and sample testing, a constant flow of small amounts of internal standards, rare earth elements, were injected into the solutions being tested. These values needed to stay within a certain range and help prove there were no erroneous test results from matrix interference. All analyses were assessed to the laboratory detection limit less than or equal to 1 µg/L. Arsenic results were disseminated to study participants after ICP-MS testing was performed; participants were delivered a letter by a study team member with their signature as proof of receipt.

## **Objective 2: Intensive Water Quality Assessment in 29 Households (2015)**

In addition to arsenic, the following additional water quality parameters were tested in 29 households in 2015: arsenic speciation, nitrate, iron, sulfate, phosphorus, alkalinity, silica, pH, uranium, cadmium, and lead. The testing parameters were selected based on historic Indian Health Service data and known compounds that interfere with filtration <sup>16</sup>. Nitrate, iron, sulfate, phosphorus, alkalinity, and silica water samples were brought back to a semi-controlled temporary laboratory and tested on a Hach DR 2800 portable spectrophotometer at the end of every sampling day. For silica samples that were over the limit of detection, a 1:100 dilution with deionized water was performed. Lead, uranium, cadmium, arsenic, and arsenic speciation water samples were stored at room temperature in a dry lab and shipped back to Johns Hopkins University Trace Metals Laboratory for ICP-MS analysis. The samples were acidified in a 1:1 dilution with 10%

optima grade HNO<sub>3</sub> (Fisher Scientific, Columbia MD) and allowed to digest at room temperature for 48 hours. The acidified samples were diluted with 2% HNO<sub>3</sub> and 0.5% HCl (Fisher Optima Trace Element Grade) in ultra-pure Milli-Q water and vortexed prior to analysis. A calibration curve for the element tested (As, Pb, Cd, U) was built using an appropriate element standard solution (Multi-element Aqueous CRM, QC Standard 21. VHG Labs, Manchester, NH, US). Ge, In and Bi were added as an internal standard (CPI International, Santa Rosa, CA, US) for samples and calibration curves to control potential drifts in the elements tested signal. All elements were analyzed using ICP-MS (Agilent 7500ce Octopole ICP-MS, Agilent Technologies, Santa Clara, CA, US). For quality control purposes, a drinking water standard reference material was used (Standard B Water TMDW-B, High Purity Standards, Charleston, SC, US). The results of the QCs were within  $\pm 10\%$  of the stated value. Ten-percent of reagent blanks and duplicates were also carried out for quality control. To measure the arsenic species arsenite (As<sup>III</sup>) and arsenate (As<sup>V</sup>), syringe filters (Millipore PVDF Sterile Syringe Filter Unit, 0.45 Micron, 33mm Diameter) and arsenic speciation cartridges (MetalSoft Center) were used.

In sub-objective 1, arsenic rapid testing kits were chosen to be tested in 23 households in 2015 because of their potential ability to inexpensively measure arsenic in drinking water in 12 minutes and identify affected households. The Econo-Quick<sup>™</sup> test brand was selected because previous studies conducted found high accuracy<sup>8, 17-21</sup>. Two Arsenic Econo-Quick<sup>™</sup> test kits were evaluated: a low-range (<1 – >160  $\mu\text{g/L}$ ) (kit # 481303) and high-range (0 – 1000  $\mu\text{g/L}$ ) (kit # 481298). The test utilizes a modified Gutzeit method: inorganic arsenic compounds present in water samples are converted to arsine gas which reacts with mercuric bromide on the test strip to form mixed mercury

halogens causing a color change from white to yellow or brown <sup>21, 22</sup>. The test is qualitative, with the color intensity proportionally related to the arsenic concentration in the sample. The color on the test strip is visually compared against a colorimetric standard (Figure 1) by the tester.

Even though recommended by the manufacturer, we did not use reagent #2 because of health concerns due to potassium peroxymonosulfate and potassium peroxydisulfate, which may cause irritation to skin or eyes or breathing difficulties if inhaled <sup>23, 24</sup>. The practice of removing reagent #2 has shown high accuracy in comparison to ICP-MS measurements previously in Bangladesh <sup>25</sup>. To manage waste in the field, our research team separated the reagents from the liquid, once tests were completed, using a coffee filter over a 5-gallon plastic bucket <sup>26</sup>, separating out the zinc and stopping production of hydrogen and arsine gases. The used filters were stored in a plastic bag for future hazardous waste disposal. One team member ran a high-range test and one team member ran a low-range test at each household, for a total of two tests per household. Testers were blinded to the results of the other.

To assess for a potential batch effect of the rapid test kits, laboratory experiments were performed with arsenic-spiked samples of known concentrations using the same kits that were used in field experiments. Five samples of Milli-Q water were spiked with sodium arsenate dibasic heptahydrate to concentrations of: 1, 5, 10, 20, and 50 µg/L. The prepared samples were prepared under strict and well-established laboratory conditions but were not tested by ICP-MS. One tester, blinded to the arsenic levels, tested each of the low-range and high-range tests twice (N=32) with (n=16) and without (n=16) reagent #2.

### **Objective 3: Efficacy of Point-of-use Filter in Study Households (2017-2018)**

The Multipure® (Model CB-As-SB, Las Vegas, NV) Drinking Water System is a point-of-use adsorptive media filter tested according to NSF/ANSI Standard 53 for the reduction of arsenic. The filter utilizes block carbon to remove arsenate (As(V)) and has a relatively high flowrate. It was installed in 6 households, a convenience sample, with water As > 10 µg/L as a pilot study in 2017. The system consists of a small filter faucet connection at the kitchen sink that is separate from the kitchen faucet that is used for washing dishes and other household tasks unrelated to drinking and cooking. The filters were monitored for nine months, with total water usage monitored and arsenic samples taken at installation and 9-month follow-up, to examine efficacy of reducing arsenic in the study setting and to determine filter life in proportion to the amount of water being used.

### **Statistical Analysis**

Objective 1: Using the fishnet tool in ArcGIS 10.5.1 (ESRI, Redlands, CA), a 5-mile by 5-mile grid of polygons was created for the three communities. The spatial join tool was used to connect the location of private wells to polygons in the grid. The averages of arsenic concentrations of wells within the same polygon was calculated for each polygon to anonymize wells. If a private well had been tested multiple times in the years 2014-2018, the highest arsenic concentration was used. For wells with arsenic concentrations below the detectable of 1 µg/L, 0.5 µg/L was used for the average

calculation. Polygons were shaded based on the range ( $<5 \mu\text{g/L}$ ;  $5 - <10 \mu\text{g/L}$ ; or  $\geq 10 \mu\text{g/L}$ ) in which the average fell.

Objective 2: Descriptive statistics were shown for water parameters and stratified by community, and differences in those characteristics in water samples by arsenic concentration ( $<10$  and  $\geq 10 \mu\text{g/L}$ ) using t-tests were compared. To estimate variability in arsenic levels in the subset of drinking water samples collected in 2014 and 2015, we estimated the intraclass correlation coefficient and used a paired t-test to estimate the mean difference between paired samples. We also estimated the Spearman's rank correlation coefficient for descriptive purposes. Statistical analyses were performed using Stata software, version 13.1 (StataCorp, College Station, TX, USA). Sub-objective 1: Determining the accuracy of the rapid arsenic testing kit provides an estimate of its usefulness as a screening tool, the weighted average of a test's sensitivity and specificity, where the sensitivity is weighted by prevalence and specificity is weighted by the complement of prevalence <sup>27</sup>. The sensitivity of the rapid test, the true positive, is defined as the proportion of wells with elevated arsenic ( $10 \mu\text{g/L}$ ) that are correctly identified by the rapid test. The specificity of the rapid test, the true negative, is defined as the proportion of wells that do not have elevated arsenic that are correctly identified as negative by the rapid test <sup>28</sup>. Sensitivity and specificity were calculated by comparing rapid test results to ICP-MS, the reference method for arsenic assessment <sup>8, 17, 19</sup>.

Objective 3: Descriptive statistics were used to compare water As levels at baseline and over the follow-up.

## RESULTS

### Objective 1: Water Arsenic Levels

Water arsenic was  $\geq 10$   $\mu\text{g/L}$  in 97 (26.1%) households, between 5 -  $<10$   $\mu\text{g/L}$  in 135 (36.4%) households, and  $<5$   $\mu\text{g/L}$  in 139 (37.5%) households, based on ICP-MS testing (Table 1, Figure 2). In Community A (n=330), 26.7% of households had water arsenic  $\geq 10$   $\mu\text{g/L}$ , with median (interquartile range [range]) arsenic of 6.6 (4.5, 10.7 [ $<1.0$ , 198.0])  $\mu\text{g/L}$ ; in Community C (n=17), 47.1% of households had water arsenic  $\geq 10$   $\mu\text{g/L}$ , with median arsenic 9.7 (3.1, 19.9 [ $<1.0$ , 30.1])  $\mu\text{g/L}$ ; and in Community B (n=24), 1 household had water arsenic  $\geq 10$   $\mu\text{g/L}$ , with median arsenic below the limit of detection (range [ $<1.0$ , 1.3])  $\mu\text{g/L}$ .

### Objective 2: Detailed Water Quality Assessment in 29 Households

Water arsenic was  $\geq 10$   $\mu\text{g/L}$  in 37.9% (n=11) in the 29 households included in the water quality assessment, with a median (interquartile range [range]) of 6.3 ( $<1.0$ , 15.0 [ $<1.0$ , 49.7])  $\mu\text{g/L}$  arsenic overall (Table 2). All parameters were similar in samples with arsenic above and below 10  $\mu\text{g/L}$ , except for sulfate which was borderline statistically higher in samples with lower arsenic concentrations (91.2 (lower arsenic) vs. 20.0 (higher arsenic) mg/L,  $p=0.07$ ). Median silica was highest in Community A (194.4 mg/L), much higher than Community B (7.96 mg/L) (Supplemental table 1). Community A also had the highest median uranium level (6.4  $\mu\text{g/L}$ ) (Supplemental table 1). Uranium was at or above the MCL (30  $\mu\text{g/L}$ ) in three wells in the 2015 pilot, with two located in Community A. Median uranium level was higher in water samples with arsenic  $\geq 10$  vs.  $<10$   $\mu\text{g/L}$  (uranium 4.4 vs. 2.9  $\mu\text{g/L}$ ,  $p=0.89$ ), but the difference was not statistically



significant (Table 2). Nitrate, iron, and cadmium medians were all below the EPA MCL and Secondary Drinking Water Standards. While lead was detectable in all three communities (highest median concentration in Community B (0.6 µg/L)), all samples were below the lead action level (EPA Treatment Technique) of 15 µg/L. For arsenic speciation, the mean percent of total arsenic that was arsenite (As(III)) was 5.0% in Community A and 38.2% in Community C (results not shown). We found some temporal variability of arsenic in wells (n=19) with ICC (95% confidence interval) of 0.77 (0.58, 0.96) and paired mean difference (95%CI) of 3.50 (0.07, 6.92) µg/L higher arsenic in 2014 vs. 2015 (Figure 3). The Spearman correlation coefficient between samples collected in 2014 and 2015 was  $r=0.86$  ( $p=0.05$ ).

In a field setting, the Arsenic Econo-Quick™ low-range test had 25.0% sensitivity and 100.0% specificity when compared to ICP-MS measurements relative to  $\geq 10$  µg/L, and the high-range test had 100.0% true positive rate and 8.3% true negative rate (Supplemental table 2 and Supplemental figure 1). In laboratory experiments with arsenic-spiked samples overall, the high-range test had moderate to high sensitivity (87.5%) and high specificity (100%); the low-range test had moderate sensitivity (62.5%) and high specificity (100%) (Supplemental table 3). The sensitivity was higher for both the high-range (100.0%) and low-range test (75.0%) when reagent 2 was not used.

### **Objective 3: Adsorptive filter results**

The Multipure® filter effectively removed arsenic in each household, with arsenic found to be below the LOD ( $<1$  µg/L) in water samples collected from each filter faucet at the installation and the 9-month follow-up timepoint (Figure 4). In the pilot

households, total water usage from the filter over 9 months ranged from 80 to 1,233 gallons (median 330). Silica ranged from 21.5 to 32.4 mg/L (median 22.6) in kitchen faucets pre-installation of the filter.

## **DISCUSSION**

### **Arsenic**

Overall, a quarter of private wells tested in tribal communities in North and South Dakota had arsenic  $\geq 10$   $\mu\text{g/L}$ , and therefore are eligible to participate in the SHWS, which will provide arsenic-safe drinking water to affected households. This is much higher than the national average of 7% of domestic well users in the US with arsenic  $\geq 10$   $\mu\text{g/L}$ <sup>1</sup>. These findings are consistent with historic Indian Health Service data for the area and with urinary arsenic excretion patterns in Strong Heart Study participants<sup>6</sup>, demonstrating that tribal communities in North Dakota and South Dakota are disproportionately exposed to arsenic in drinking water, especially in Communities A and C. Community C is undergoing the installation of a new public water system that will provide service to homes on private wells, including many of those tested in this water quality assessment. As such, the SHWS will focus on Community A, where homes often cannot be connected to community water systems, typically because of distance from the tribal water system line, and arsenic-safe drinking water is urgently needed. The Multipure® filter was found to be highly effective at lowering drinking and cooking water arsenic concentrations below 1  $\mu\text{g/L}$ , even after consistent usage over 9 months. As a result, this point-of-use arsenic removal device will be used to reduce arsenic exposure in the SHWS intervention.

## **Water Quality Parameters**

Silica was above the manufacturer's recommended concentration for optimal filter performance ( $<30$  mg/L) in 20 households out of 29 in the 2015 intensive water quality pilot and in 1 household out of 6 where the filter was installed<sup>29</sup>. High silica concentrations could reduce the amount of time the filter will effectively be able to remove arsenic, consequently increasing the frequency that the filter cartridge will need to be replaced.<sup>30</sup> Our pilot study showed that the adsorptive media filter proposed for the SHWS effectively removed As for 9 months, indicating that the well with high silica in Community A did not affect the performance of the filter. Sulfate and iron can also potentially interfere with an adsorptive media water filter. However, the levels of sulfate and iron found at study communities were below the problem levels for both parameters (720 mg/L and 0.5 mg/L, respectively)<sup>16</sup>. The majority of inorganic arsenic in the study communities occurred as As(V), which is considered less toxic than As(III)<sup>5</sup>. Reverse osmosis was not chosen as a treatment option, as treated water may substantially change the taste of household drinking water since during the treatment process inorganic compounds are removed, and during our formative research, community members expressed concern about certain water filters changing the taste of their drinking water. Another concern about reverse osmosis was the relatively low flow rate.

## **Performance of the Rapid Arsenic Test**

The Arsenic Econo-Quick<sup>TM</sup> test performed poorly in our setting and cannot be used as a screening tool at our community sites. It was difficult to meet the required test

manufacturer conditions to conduct the test in the field. The manufacturer recommends water samples be warmed to 22 - 28°C before testing; air temperature is recommended to be in the same range <sup>22</sup>. At our community site, water samples were not warmed upon collection, and tests were conducted outside in November (mean air temperature 8.3°C) <sup>31</sup>. However, a study in Peru with similar cold weather conditions using the same kit found the high-range test to be accurate <sup>18</sup>. Another potential source of interference is sulfide. When reagent #2 was removed, our ability to mitigate any interference with sulfide was also removed. Sulfide concentrations at our community site were tested in February 2017 as part of the SHWS filter pilot; all sulfide levels were < 0.050 mg/L, below the 2 mg/L sulfide threshold the manufacturer reports causes interference. The rapid test needs to be used in a well-ventilated area due to the production of hydrogen and arsine gases, in addition to eye and hand protection <sup>22</sup>. Disposal of waste presented a problem for team members while conducting field work, as both liquid waste and mercuric bromide testing strips needed to be properly handled. This is an additional concern in resource limited settings where waste disposal facilities are not available.

### **Arsenic Temporality**

In the 19 households that had arsenic samples taken in both 2014 and 2015, findings suggest some temporal variability of the arsenic levels in groundwater over our one-year surveillance period, with levels being on average slightly lower in the 2<sup>nd</sup> period. Other studies have shown that the degree of temporal variability in groundwater arsenic is generally low <sup>32, 33</sup>. The arsenic concentration variability that we found could have arisen from seasonal effects, or anthropogenic reasons, like aquifer pumping <sup>34</sup>.

### **Multipure® filter**

The Multipure® filter effectively removed arsenic in each household that participated in the pilot study to below 1 µg/L at the 9-month follow-up, including one household that had elevated silica, and is an adequate water treatment intervention for the SHWS. For private well users, point-of-use filtration devices have been shown to be effective in removing arsenic from drinking water, and major challenges are consistent use of the filter and maintenance over time <sup>35,36</sup>. The SHWS engages community promoters to deliver messages on the importance of using the filter faucet for drinking and cooking, and to explain to households how to change the filter cartridge for their arsenic removal device.

### **CONCLUSIONS**

This water quality assessment and pilot of a point-of-use arsenic removal device was important for informing the next steps of the Strong Heart Water Study, the first randomized controlled trial of a community based arsenic mitigation intervention in the US. We identified that arsenic above the current arsenic MCL in drinking water was relatively common, especially in communities A and C. We also found elevated silica, which could reduce the efficacy of a point-of-use arsenic absorptive media filter. The Arsenic Econo-Quick™ test, originally planned for use as a screening tool for recruitment of participants in the intervention, was found to have low performance in rural North Dakota and South Dakota. In our assessment of the effectiveness of the adsorptive media water filtration device for arsenic removal, all devices installed removed arsenic below 1

µg/L at both installation and 9 months post-installation. Through our water quality assessment, we identified a relatively high burden of arsenic as well as an effective water filtration device to reduce arsenic exposure in study communities. The long-term efficacy of a community-based arsenic mitigation program, including these arsenic removal devices in reducing arsenic exposure and preventing arsenic related disease, is being tested as part of the ongoing intervention study.

## TABLES

**Table 1. Water Arsenic (µg/L) in Domestic Wells in SHWS Tribal Nations in 2014-2018 (N= 371)**

	<b>All</b>	<b>Community A</b>	<b>Community B</b>	<b>Community C</b>
N	371	330	24	17
Median (IQR)	6.3 (4.0, 10.5)	6.6 (4.5, 10.7)	<1.0* (<1.0*, <1.0*)	9.7 (3.1, 19.9)
Range	<1.0*, 198.0	<1.0*, 198.0	<1.0*, 1.3	<1.0*, 30.1
Number of wells:				
< 5 µg/L	139	111 (79.9%)	23 (16.5%)	5 (3.6%)
≥ 5- <10 µg/L	135	131 (97.0%)	0	4 (3.0%)
≥ 10 µg/L	97	88 (90.7%)	1 (1.0%)	8 (8.2%)

\*Limit of detection

**Table 2. Median Concentration (IQR) of Water Parameters Tested in 29 Households Overall and by Water Arsenic Levels Above and Below 10 µg/L**

Parameter <sup>c</sup>	N	Limit of detection <sup>a</sup>	Median (IQR)	Median		P value*	Analytical method	Analytical location
			Overall	As <10 µg/L	As ≥10 µg/L			
Arsenic (µg/L)	29	0.1	6.3 (0.3-15.0)				ICP-MS	JHU Trace Metals lab
Cadmium (µg/L)	29	0.0052	0.005 (0.005-0.005)	0.01	0.01	0.41	ICP-MS	JHU Trace Metals lab
Iron (mg/L)	29	0.2 <sup>b</sup>	0.1 (0.1-0.1)	0.1	0.1	0.71	Hach	Semi-controlled temp. lab
Lead (µg/L)	29	0.0029	0.49 (0.15-0.42)	0.3	0.1	0.14	ICP-MS	JHU Trace Metals Lab
Phosphorus (mg/L)	24	0.05 <sup>b</sup>	0.025 (0.025-0.11)	0.03	0.03	0.63	Hach	Semi-controlled temp. lab
Silica (mg/L)	27	0.01 <sup>b**</sup>	107.2 (14.4-162.4)	109.2	107.2	0.69	Hach	Semi-controlled temp. lab
Uranium (µg/L)	29	0.0015	3.42 (0.32-6.38)	2.9	4.4	0.89	ICP-MS	JHU Trace Metals lab
Nitrate (mg/L)	29	0.2 <sup>b</sup>	0.33 (0.1-0.79)	0.2	0.5	0.61	Hach	Semi-controlled temp. lab
Sulfate (mg/L)	29	40 <sup>b</sup>	41.5 (20-143)	91.2	20.0	0.07	Hach	Semi-controlled temp. lab
Alkalinity (mg/L)	29	25 <sup>b</sup>	214 (153-278)	214.0	230.0	0.68	Hach	field
pH	29	0 <sup>b</sup>	6.8 (6.5-7.1)	6.7	6.9	0.27	YSI	field

<sup>a</sup> Limit of detection (LOD) = LOD/2 (used in analyses) for undetectable samples;

<sup>b</sup> Upper limit: phosphorus = 1.50 mg/L; silica = 1.60 mg/L; nitrate = 30.0 mg/L; sulfate = 150 mg/L; alkalinity = 400 mg/L; iron = 6.0 mg/L; pH = 14 units

<sup>c</sup> US Environmental Protection Agency's National Primary Drinking Water Regulations, maximum contaminant level (MCL): arsenic = 0.010 mg/L; cadmium = 0.005 mg/L; lead = zero; uranium = zero; nitrate = 10 mg/L

\* P-value comparing difference in parameter between low and high arsenic.

\*\* For samples over the limit of detection, measurement performed by 1:100 dilution with deionized water

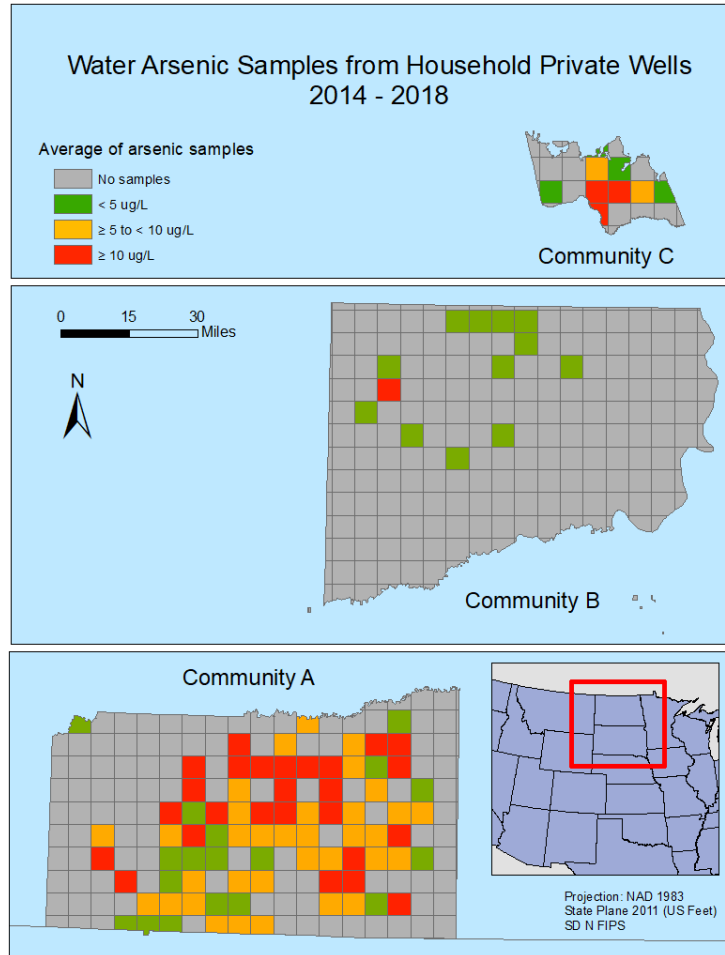


## FIGURES

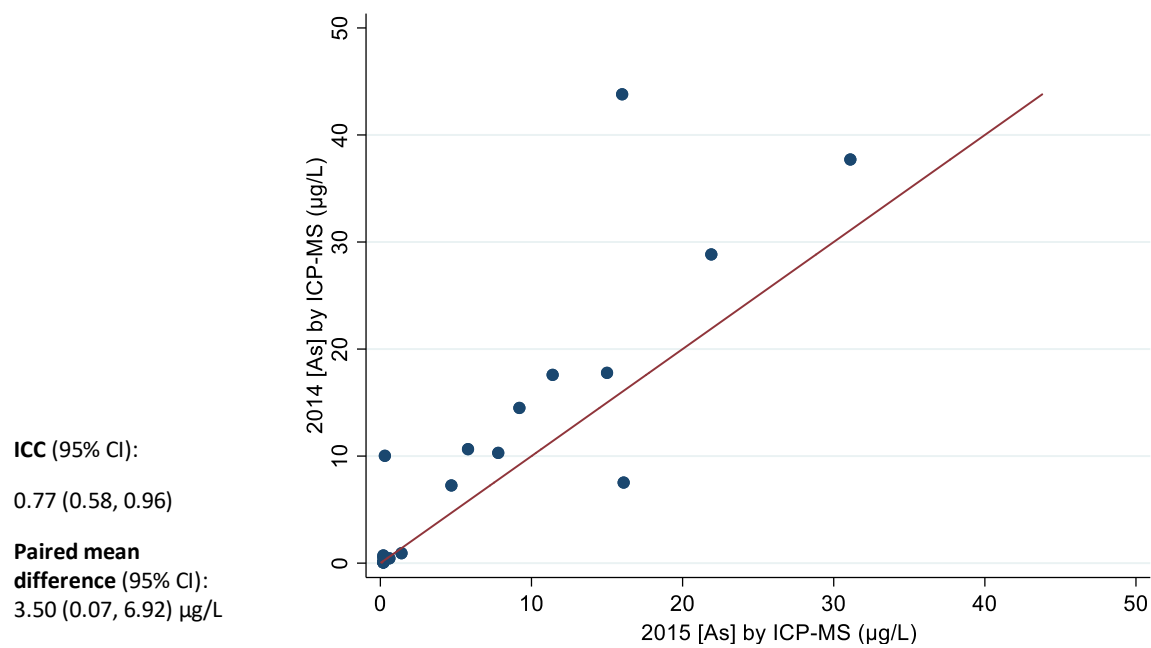
**Figure 4. Visual comparison of test strip from Arsenic Econo-Quick™ test against colorimetric standard to determine water arsenic concentration.**



**Figure 5. Water Arsenic Samples from Household Private Wells in SHWS Tribal Nations from 2014-2018.** The total number of samples was 330 in Community A, 24 in Community B, and 17 in Community C. The mean water arsenic concentrations were estimated in a 5-mile by 5-mile grid of polygons to anonymize wells. The number of samples in each polygon ranged from 1 to 20 (median: 2).



**Figure 6. Comparison of 2014 and 2015 ICP-MS arsenic measurements (n=19) in SHWS study sites.**



**Figure 4. Arsenic concentration at baseline and 9-month follow-up with detection limit line at 1.0  $\mu\text{g/L}$  (N= 6 households)**



## SUPPLEMENTAL MATERIAL

**Supplemental table 1S. Median (Interquartile Range) Concentration of Water Parameters by Community in 29 Households**

	Community A	Community B	Community C
N	11	9	9
Arsenic (µg/L)	11.4 (5.8, 16.1)	0.2 (0.2, 0.2)	11.4 (6.3, 22.3)
Cadmium (µg/L)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)
Iron (µg/L)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)
Lead (µg/L)	0.2 (0.1, 0.3)	0.6 (0.3, 1.0)	0.2 (0.2, 0.3)
Nitrate (mg/L)	0.9 (0.5, 1.4)	0.1 (0.1, 0.6)	0.1 (0.1, 0.1)
Uranium (µg/L)	6.4 (3.4, 24.0)	0.3 (0.1, 2.7)	2.6 (0.9, 4.4)
Phosphorus (mg/L)	0.03 (0.03, 0.03)	0.1 (0.08, 0.1)	0.06 (0.03, 0.1)
Silica (mg/L)	194.4 (119.4, 274.1)	7.9 (4.7, 14.4)	107.2 (101.7, 124.9)
Sulfate (mg/L)	20.0 (20.0, 143.0)	118.0 (20.0, 347.5)	47.9 (20.0, 140.0)
pH	6.8 (6.5, 7.1)	6.6 (6.3, 7.2)	6.9 (6.5, 7.0)
Alkalinity (mg/L)	209.0 (122.0, 236.0)	206.0 (153.0, 280.0)	275.0 (226.0, 278.0)

**Supplemental table 2S. Accuracy of Rapid Test in Field Setting Compared to ICP-MS to Identify Samples  $\geq 10$   $\mu\text{g/L}$**

	True positive rate (Sensitivity)*	95% CI	True negative rate (Specificity)**	95% CI	Accuracy
<b>Low-range test (N=22)</b>					
$\geq 10$ $\mu\text{g/L}$	25.0% (2/8)	3.2 – 65.1%	100.0% (14/14)	76.8 - 100.0%	72.7% (16/22)
$\geq 5$	62.5% (5/8)	24.5 – 91.5%	92.9% (13/14)	66.1 – 99.8%	81.8% (18/22)
$\geq 3$	100.0% (8/8)	63.1– 100.0%	85.7% (12/14)	57.2 – 98.2%	90.9% (20/22)
<b>High-range test (N=19)</b>					
$\geq 10$	100.0% (7/7)	59.0 - 100.0%	8.3% (1/12)	0.0 - 26.5%	42.1% (8/19)

\*The true positive rate (sensitivity) is the ratio of true positive/(true positive+false negative).

\*\*The true negative rate is the ratio of the true negative /(true negative + false positive).

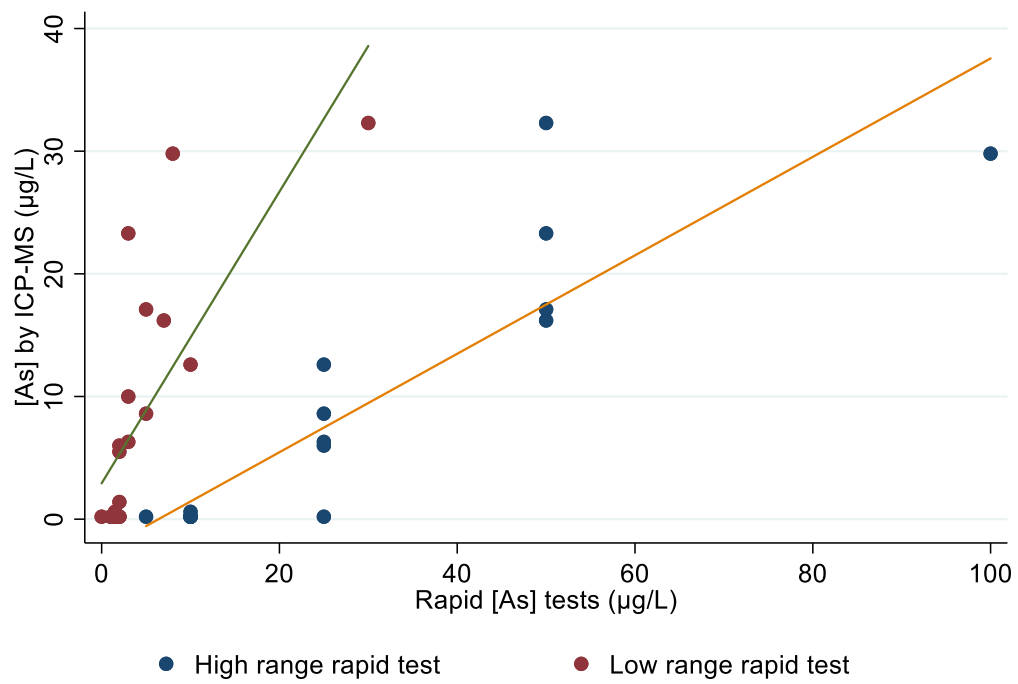
**Supplemental table 3S. Accuracy of Rapid Test in Laboratory Setting to Identify Samples  $\geq 10 \mu\text{g/L}$**

	True positive rate (Sensitivity)*	95% CI	True negative rate (Specificity)**	95% CI
<b>Low-range test (N=16)</b>	62.5% (5/8)	24.5 – 91.5	100.0% (8/8)	63.1 – 100.0
No reagent 2 (n=10)	75.0% (3/4)	19.4 – 99.4	100.0% (6/6)	54.1 – 100.0
With reagent 2 (n=6)	50.0% (2/4)	6.8 – 93.2	100.0% (2/2)	15.8 – 100.0
<b>High-range test (N=16)</b>	87.5% (7/8)	47.4 – 99.7	100.0% (8/8)	63.1 – 100.0
No reagent 2 (n=10)	100.0% (4/4)	39.8 – 100.0	100.0% (6/6)	54.1 – 100.0
With reagent 2 (n=6)	75.0% (3/4)	19.4 – 99.4	100.0% (2/2)	15.8 – 100.0

\*The true positive rate (sensitivity) is the ratio of true positive/(true positive+false negative).

\*\*The true negative rate is the ratio of the true negative /(true negative + false positive).

**Supplemental figure 1S. Arsenic measurements by Rapid Tests in a Field Setting and by ICP-MS (N=41)**





## DISCUSSION

### Summary of Findings

The main objectives of this dissertation were to (1) evaluate the relationship between arsenic exposure and nonmalignant respiratory health in a population chronically exposed to low-moderate arsenic levels; (2) evaluate the impact of tuberculosis survival on lung function and its potential association with arsenic exposure in the Strong Heart Study; and (3) conduct water arsenic testing and a water quality assessment pilot for the Strong Heart Water Study. This dissertation attempted to examine the relationship between low-moderate arsenic exposure and respiratory outcomes given widespread exposure to arsenic through drinking water in the study population and the availability of multiple measures of respiratory health status.

In Chapter 1 we conducted multiple analyses using data from the Strong Heart Study (SHS) in order to examine the association between arsenic exposure and nonmalignant respiratory outcomes. We first evaluated differences in participant variables by spirometric obstruction and restrictive patterns and urinary arsenic tertile. We then estimated the odds ratio for the presence of an obstructive or restrictive pattern, using both the fixed-ratio and lower-limit of normal definitions, respiratory symptoms, and nonmalignant respiratory disease by urinary arsenic concentration. We also assessed the mean difference of FEV1, FVC, and FEV1/FVC using both % predicted values and crude mL values. In all models, we ran sensitivity analyses for outcomes by further adjusting for diabetes. We evaluated effect modification for the association of arsenic with obstruction and restrictive pattern by indicator variables for sex, age, smoking status, body mass index, and diabetes. We also evaluated arsenic metabolism by

examining the association between the relative proportions of arsenic species (iAs%, MMA% and DMA%) in urine per 5% change with the presence of an obstructive or restrictive pattern. Arsenic was associated with increased odds of fixed-ratio restrictive lung pattern, lower FEV1 and lower FVC (both % predicted and crude values), borderline associated with fixed-ratio obstruction, and not associated with FEV1/FVC. These findings support recent meta-analysis findings that low-level arsenic exposure is a restrictive lung disease risk factor. Urinary relative proportions of iAs, MMA, and DMA were not associated with an obstruction or restrictive pattern. Arsenic was associated with the symptom ‘stopping for breath while walking’ and with self-reported emphysema. However, in the sensitivity analyses, diabetes attenuated the association of arsenic with restrictive pattern suggesting the possibility that diabetes could be in the causal pathway between arsenic and restrictive lung disease.

In Chapter 2 we examined the lung health of individuals in the SHS who previously had been treated for active tuberculosis in order assess the morbidity of nonmalignant respiratory effects when compared to those without a history of active tuberculosis. We used data from a medical record-based history of active tuberculosis, spirometric measures, and self-reported respiratory symptoms from the Visit 2 examination (1993-1995) in 2,463 participants, adjusting for major lung health risk factors including smoking and cigarette pack-years. We also conducted a sub-analysis to examine the potential association between a history of active tuberculosis and arsenic exposure as well as a possible interaction between arsenic and tuberculosis on spirometric obstruction and restrictive patterns. In those with a history of active tuberculosis, lung function and respiratory symptoms were worse compared to those without active

tuberculosis, including a reduced FEV1 % predicted and FVC % predicted, and an increased odds of spirometric obstruction and restrictive pattern. A dose-response relationship was seen for decreasing lung function indices FEV1 % predicted and FVC % predicted in those with a history of active tuberculosis by increasing urinary arsenic concentrations, as expected, but elevated arsenic exposure was associated with a reduced odds of a past history of active tuberculosis, an unexpected finding.

In Chapter 3 we conducted a water quality assessment in preparation for the Strong Heart Water Study (SHWS) intervention to identify households with private wells with elevated arsenic, using inductively coupled plasma mass spectrometry, that are eligible for the SHWS; assess water quality parameters that could interfere with the efficacy of the adsorptive media filter; evaluate the accuracy of a rapid testing kit for arsenic; and evaluate the efficacy of the adsorptive media filter. Water samples (n= 371) were collected from domestic wells between 2014 – 2018 in study communities where 26.1% of households were found to have arsenic higher than 10 µg/L, with the majority of arsenic occurring as arsenate (As(V)). In 2015, a more detailed water quality assessment was conducted in a subset of households where rapid arsenic tests were used, and additional water quality parameters were examined for possible compounds that interfere with an arsenic filtration device. The rapid test kits were not sufficiently accurate in the study setting, and silica was found to be above the concentration for optimal filter performance. Finally, we evaluated the efficacy of an adsorptive media filter for its ability to remove As(V) at the kitchen sink in six households. After being monitored for nine months, the filters were found to reduce arsenic to below the limit of detection (<1 µg/L).

## Unexpected Findings

In Chapter 1, we observed a significant relationship between arsenic and spirometric obstruction only in former cigarette smokers, as compared to never and current smokers, which was not expected. As smoking is a major cause of lung obstruction, we anticipated that we would see the strongest effect estimates in current smokers. A small number of previous studies have reported similar findings, specifically examining lung function indices,<sup>1,2</sup> with conjecture that active smoking's toxic effects could be masking those of arsenic. Studies which have examined the interaction between smoking, arsenic, and lung cancer have generally found the presence of a synergistic interaction, that the excess risk resulting from the combination of exposure to smoking and arsenic is greater than the sum of excess risks from each exposure alone.<sup>3,4</sup> There is less known about nonmalignant lung disease outcomes; a recent meta-analysis found the association between arsenic and FVC to be slightly stronger among non-smokers than smokers, for reasons unknown.<sup>5</sup>

Additionally, in Chapter 1, we did not find an association with lung function patterns and arsenic metabolism, which was unexpected as arsenic metabolism has been related to multiple health outcomes. After ingestion, arsenic is metabolized into mono- and di-methylated arsenicals (MMA and DMA).<sup>6</sup> The methylation of inorganic arsenic to DMA facilitates its excretion and detoxification, with findings often showing that a higher percentages of DMA and lower MMA in the urine is associated with reduced arsenic-related health effects, including cardiovascular disease and cancer<sup>7</sup> with some evidence of lung cancer.<sup>8,9</sup> Lung cancer studies have shown that individuals who are less

effective at methylating MMA to DMA are at increased risk of lung cancer at water arsenic exposure levels of  $<200\text{ }\mu\text{g/L}$ . While we expected to possibly see an indication of restrictive or obstructive spirometric pattern associated with arsenic methylation similar to that of what has been seen with lung cancer, the majority of individuals in the lung cancer studies were exposed to water arsenic concentrations much higher than  $10\text{ }\mu\text{g/L}$ , and thus perhaps less comparable to the SHS population.<sup>8,9</sup>

In our additional analysis in Chapter 2, we found a statistically significant reduced odds of a past active tuberculosis diagnosis associated with arsenic exposure, which was unexpected. The finding is inconsistent with the one earlier study from Chile which also examined the relationship between tuberculosis and arsenic.<sup>10</sup> This previous ecological study found increased mortality from pulmonary tuberculosis associated with arsenic levels in drinking water, with mortality rates increasing ten years after high arsenic exposure ( $870\text{ }\mu\text{g/L}$ ) commenced. Our finding of a reduced odds of tuberculosis could be an effect of survival bias, as more severe tuberculosis cases may have resulted in mortalities prior to the start of the SHS; we could be over-representing those with long-term survival after treatment for tuberculosis, particularly as advanced age, diabetes, and chronic obstructive pulmonary disease have been shown to be associated with an increased risk of death during tuberculosis treatment,<sup>11</sup> risk factors very relevant to our cohort. We could not determine if arsenic could have increased the incidence of active tuberculosis or increased the mortality among those with tuberculosis, which could also spuriously result in an inverse association similar to the one that we observe. Even with our unexpected finding of reduced odds, we know to interpret it cautiously as both arsenic and tuberculosis are both known to be associated with an increased risk of

developing bronchiectasis. This suggests a potential common pathophysiology for the long-term impact of arsenic and tuberculosis on lung disease.<sup>12-14</sup> This common pathophysiology can actually support the synergistic interaction we observed between past active tuberculosis and arsenic exposure on lung outcomes.

In Chapter 3, our finding that a low-range field rapid arsenic testing kit had low accuracy and, therefore, not an option as a screening tool for the SHWS intervention was unexpected. As the same rapid testing kit had been found to be accurate in previous studies,<sup>15-20</sup> the test was planned to be used as a way to help develop local expertise on testing water sources so that there would be long-term sustainability of arsenic water testing conducted by community members, especially as most private well users in these communities are unknowingly at risk of elevated arsenic exposure due to lack of access to water testing services. An original goal of the SHWS intervention was that the rapid test kit could be used by a field team with minimal training to accurately measure water arsenic levels rapidly, give feedback to family and enroll the households into the study if they were eligible. Due to its poor performance, the rapid test kit cannot be used as a screening tool for the SHWS. Instead, ICMPS, which is highly accurate and sensitive, was used as the sole method for arsenic detection.

### **Strengths and Limitations**

This dissertation benefitted from several strengths. The SHS is a well-established cohort with high-quality laboratory methods, high participant retention, consistent variable collection, careful outcomes determination, and strong support from the communities involved. We had individual spirometric measurements standardized to

American Thoracic Society recommendations. We also had American Indian reference values derived from the SHS cohort, which allowed for results to be evaluated for abnormalities against predicted values for better interpretation of results. However, the subgroup used to calculate predicted values, while comprehensive in excluding those with respiratory disease, symptoms, and comorbidities, did not exclude those individuals with high arsenic exposure. This is unlikely to be a major limitation as lung function measures across arsenic tertiles showed similar trends when using % predicted values vs. crude (mL) values (Chapter 1, Table 5). We were able to adjust models for the more prevalent and important risk factors for lung health, including smoking status and cigarette pack-year; however, these measures were self-reported as we did not have a biomarker of tobacco exposure. A strength was that we had the unique opportunity to apply our respiratory health findings from the SHS to the SHWS. The SHWS is the first study to evaluate the effectiveness of an intervention approach to reduce arsenic exposure in American Indian communities, so that we can ultimately examine respiratory health before and after installation of a point-of-use water arsenic filter.

As in all epidemiological studies, several limitations affected the results and interpretations of this thesis. In Chapter 3, our evaluation of the rapid arsenic testing kit was limited to a very small subset in the SHWS, making it difficult to make broad conclusions from our results and prohibiting external validity outside of our study communities in rural North Dakota and South Dakota. In Chapters 1 and 2, we lacked information on possible exposure to indoor air pollutants, including secondhand smoke and exposure to smoke from cooking fires or heating fuel, potentially important contributors to lung health were unadjusted for in models. Spirometry reliability could

have impacted our results. A measure of total lung capacity is recommended in clinical practice to diagnose restrictive lung disease. In lieu of this measurement, FVC is used in population-based epidemiological studies, and can result in low sensitivity and poor specificity in identifying restrictive patterns.<sup>21</sup> There has been technological improvement in spirometric methodology, as the change in test session repeatability criteria has reduced from the 1994 level of <200 mL to <150 mL, per ATS/ERS standardization recommendations.<sup>22</sup> Spirometric results from 1993-1995 in the SHS should be interpreted cautiously when comparing to any future spirometric results from the same population, considering they employed the then-current but comparatively more lenient repeatability requirement of 200 mL.<sup>23</sup> The protocol for spirometric testing in the SHS did not include post-bronchodilator testing and we were not able to assess the change over time in lung function based on post-bronchodilator testing. While urine arsenic metabolites have been shown to be consistent over time,<sup>24</sup> urine arsenic collected at multiple visits would have made our results more robust. Additionally, being able to examine spirometry at multiple visits would have made our analyses and interpretations stronger, as without longitudinal spirometric data, we were not able to determine the possible temporal relationship between arsenic exposure and lung disease.

## **Implications and Future Research**

This dissertation provides novel evidence that exposure to low-moderate arsenic may have a deleterious effect on lung function, not examined before in any American Indian population. Studies evaluating the effect of low-level arsenic exposure are critical to assist in accurately characterizing the total health risk posed by arsenic, particularly as



some states in the US are reassessing exposure level standards in drinking water.

Longitudinal studies of lung function and low-moderate arsenic are important to further examine the types of lung disease associated with arsenic exposure, the possible temporal relationship, and explore arsenic methylation as it relates to these outcomes.

Our finding that a history of active tuberculosis is a risk factor for long-term respiratory impairment confirms existing knowledge, adds evidence of the relationship from an American Indian population which is lacking in the literature base, and adds information on specific spirometric disease patterns. Our unexpected finding of reduced odds of active tuberculosis associated with arsenic exposure warrants further research to better understand this relationship. In addition to tuberculosis, future research could examine whether higher arsenic exposure is associated with repeated respiratory infections and contribution to overall respiratory health. More common respiratory infections in American Indians include coccidioidomycosis, known as valley fever, which occurs due to the inhalation of fungi spores found in soil in desert regions of the Southwest, pneumonia, and *Hemophilus influenzae*.<sup>25</sup>

Our finding of a high overall burden of spirometry-defined obstruction and restriction in the SHS is important as little has been known about the nonmalignant respiratory health in the population. Continued surveillance with spirometry is necessary for monitoring the respiratory health of the population, as morbidity for diseases like chronic obstructive pulmonary disorder is important to track, since these data can provide an estimate of the need for health services.<sup>26</sup> Through the SHWS we have the opportunity to evaluate changes in lung function using spirometry with delivery of an intervention to

reduce arsenic exposure in SHS communities. This will greatly add to our understanding of the relationship between arsenic and respiratory health.

An important finding from our water quality assessment in the SHWS was that arsenic above the current US health safety standard ( $>10 \mu\text{g/L}$ ) in drinking water is relatively common in the study communities. This, combined with our epidemiological findings on lung health, support the need for interventions like the SHWS. The finding that the rapid arsenic test kits were not accurate in the study setting meant that study procedure had to be changed, but also confirmed that the SHWS intervention has reliable data on which households have elevated drinking water arsenic and are eligible to enroll in the study.

## **Conclusions**

Chronic lung disease is among the leading causes of death worldwide, making identification of modifiable risk factors, as well as high risk populations, a public health priority. Previous studies have reported water arsenic exposure to be associated with nonmalignant respiratory health; however, most studies have occurred at high arsenic exposure levels, with few examining exposure at low-moderate ( $<50 \mu\text{g/L}$ ) arsenic levels. This dissertation adds evidence that low-moderate arsenic exposure from water is associated with reduced lung function and increased respiratory symptoms in an American Indian population. Further, we present evidence that a past history of active tuberculosis is associated with long-term pulmonary damage with suggestive evidence of a possible interaction between arsenic exposure and tuberculosis on lung function. This evidence combined with the finding of elevated arsenic being common in study

households, points to the need for prevention strategies like the SHWS intervention to protect human health at the household level. Furthermore, increased respiratory symptoms and reduced lung function from a history of tuberculosis or chronic arsenic exposure is likely contributing to an unmeasured burden of chronic lung disease. Added with the systemic underrepresentation of American Indians in published biomedical research on pulmonary disease, this indicates an urgent need for the continued monitoring of American Indian respiratory health and additional research to better understand the intersecting relationships between arsenic, tuberculosis and other respiratory infections, and lung health.

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## Chapter 1

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## Discussion

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  23. Marion M, Leonardson G, Rhoades E, Welty T, Enright P. Spirometry Reference Values for American Indian Adults: Results from the Strong Heart Study. *Chest*. 2001;120(2):489-95.
  24. Navas-Acien A, Umans JG, Howard BV, Goessler W, Francesconi KA, Crainiceanu CM, Silbergeld EK, Guallar E. Urine arsenic concentrations and species excretion patterns in American Indian communities over a 10-year period: the Strong Heart Study. *Environ Health Perspect*. 2009;117(9):1428-33. doi: 10.1289/ehp.0800509. PubMed PMID: 19750109; PMCID: PMC2737021.
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## CURRICULUM VITAE

**Martha B. Powers, MES, MPH**

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### PROFILE

Under the guidance of Dr. Ana Navas-Acien, I am studying the fields of environmental epidemiology and exposure science through the Strong Heart Study, a prospective study of cardiovascular disease in American Indians, and the Strong Heart Water Study, a randomized controlled trial intervention to reduce arsenic in drinking water.

### EDUCATION

Aug 2019

#### **Doctor of Philosophy (PhD)**

Department of Environmental Health and Engineering, Exposure Science and Environmental Epidemiology Track  
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

**Dissertation:** Low-moderate Arsenic Exposure and Respiratory Health in American Indian Communities (Dr. Ana Navas-Acien)

May 2014

#### **Master of Public Health (MPH)**

Perelman School of Medicine, Environmental Health Track  
University of Pennsylvania, Philadelphia, PA

*Capstone project:* Citizens' Concerns Regarding the Health and Social Impacts of Natural Gas Extraction (Dr. Carolyn Cannuscio)

May 2012

#### **Master of Environmental Studies (MES)**

Department of Earth & Environmental Science  
University of Pennsylvania, Philadelphia, PA

*Capstone project:* Application of Superfund Law to Emerging Natural Resource Extraction in Pennsylvania (Prof. Richard Pepino)

May 2007

#### **Bachelor of Arts in English (BA)**

Commonwealth Honors College  
University of Massachusetts- Amherst, Amherst, MA

### RESEARCH INTERESTS

Environmental epidemiology, biomarkers of exposure, Indigenous health, arsenic, translation of epidemiologic findings into interventions, community-based participatory research, environmental justice

### GRANTS

01/2018 – 12/2019 F31 NIEHS Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship- F31ESO28597, Powers (PI), \$88,088

## **PROFESSIONAL EXPERIENCE**

09/2012 – 07/2014 Undergraduate Coordinator & Geology Collections Manager  
Department of Earth & Environmental Science, University of Pennsylvania

05/2010 – 09/2012 STEER Research Coordinator, Community Engagement Core  
Center of Excellence in Environmental Toxicology (Superfund Research Program), University of Pennsylvania

10/2007 – 07/2009 Outreach & Education Coordinator  
Freshkills Park, NYC Department of Parks & Recreation, New York, NY

## **TEACHING EXPERIENCE**

2017, 2018 Teaching Assistant  
Course: Environmental Justice: Concepts, Methods, and Practice (Dr. Chris Heaney)  
Johns Hopkins Bloomberg School of Public Health

2016 – 2017 Journal Club Coordinator, Exposure Science and Environmental Epidemiology  
Johns Hopkins Bloomberg School of Public Health

2015 Teaching Assistant  
Course: Occupational & Environmental Health (Dr. Bill Spannhake)  
Johns Hopkins Bloomberg School of Public Health

2014 Teaching Assistant  
Course: Occupational and Environmental Health (Profs. Marilyn Howarth, Richard Pepino), Perelman School of Medicine, University of Pennsylvania

2010 – 2012 Teaching Assistant  
Courses: Community-based Environmental Health; Urban Environments – Speaking About Lead in West Philadelphia  
Department of Earth & Environmental Science, University of Pennsylvania

## **HONORS**

2017 Travel award, Thomas L. Petty Aspen Lung Conference, Aspen, Colorado

- 2016            Travel award, International Society for Environmental Epidemiology (ISEE) Conference, Rome, Italy
- 2016            Field placement award to Tribal Nations in North Dakota and South Dakota, Center for Global Health, Johns Hopkins Bloomberg School of Public Health
- 2007            Senior Thesis Research Grant, Commonwealth Honors College, UMass-Amherst
- 2003 – 2007   Stanley Z. Koplik Certificate of Mastery with Distinction, merit-based tuition waiver for undergraduate studies in Commonwealth of Massachusetts

## **PROFESSIONAL ORGANIZATIONS, CERTIFICATIONS AND SERVICE**

### **Society Membership:**

American Public Health Association (APHA)

International Society for Environmental Epidemiology (ISEE)

### **Certification:**

2016            Spirometry, National Institute for Occupational Safety and Health (NIOSH)

### **Peer Review Activities:**

Journal of Environmental Psychology

Environmental Research

Environment International

Annals of the American Thoracic Society

## **PUBLICATIONS (Peer Reviewed)**

1. **Powers M**, Sanchez TR, Welty T, Cole SA, Yeh F, Turner J, O’Leary M, Brown RH, O’Donnell M, Lederer D, Navas-Acien A. Pulmonary impairment after history of tuberculosis in an American Indian population. “Submitted for publication.”
2. **Powers M**, Sanchez, TR, Grau-Perez M, Yeh F, Francesconi K, Goessler W, George CM, Heaney C, Best L, Umans J, Brown RH, Navas-Acien A. Low-moderate arsenic exposure and respiratory health in American Indian communities. “Submitted for publication.”
3. Thomas ED, Gittelsohn J, Yracheta J, **Powers M**, O’Leary M, Harvey DE, Red Cloud R, Best LG, Black Bear A, Navas-Acien A, George CM. The Strong Heart Water Study: Informing and designing a multi-level intervention to reduce arsenic exposure among private well users in Great Plains Indian Nations. *Sci Total Environ*. 2019;650(Pt 2):3120-33. Epub 2018/10/31. doi: 10.1016/j.scitotenv.2018.09.204. PubMed PMID: 30373089.

4. **Powers M**, Yracheta J, Harvey D, O'Leary M, Best LG, Black Bear A, MacDonald L, Susan J, Hasan K, Thomas E, Morgan C, Olmedo P, Chen R, Rule A, Schwab K, Navas-Acien A, George CM. Arsenic in groundwater in private wells in rural North Dakota and South Dakota: Water quality assessment for an intervention trial. *Environ Res*. 2018;168:41-7. Epub 2018/09/28. doi: 10.1016/j.envres.2018.09.016. PubMed PMID: 30261340.
5. **Powers M**, Maruthur N, Howard B, Umans J, Lee E, Best LG, Navas-Acien A. Association of Urine Zinc with Prevalent and Incident Diabetes in the Strong Heart Study. "Draft under co-author review."
6. Sanchez TR, **Powers M**, Perzanowski M, George CM, Graziano JH, Navas-Acien A. A Meta-analysis of Arsenic Exposure and Lung Function: Is There Evidence of Restrictive or Obstructive Lung Disease? *Current environmental health reports*. 2018. Epub 2018/04/11. doi: 10.1007/s40572-018-0192-1. PubMed PMID: 29637476.
7. **Powers M**, Saberi P, Pepino R, Strupp E, Bugos E, Cannuscio CC. Popular Epidemiology and "Fracking": Citizens' Concerns Regarding the Economic, Environmental, Health and Social Impacts of Unconventional Natural Gas Drilling Operations. *J Community Health*. 2014 Nov 13;40(3):534–41.
8. Saberi P, Probert KJ, **Powers M**, Emmett E, Green-McKenzie J. Field Survey of Health Perception and Complaints of Pennsylvania Residents in the Marcellus Shale Region. *International Journal of Environmental Research and Public Health*. 2014; 11(6):6517-6527.
9. Pak VM, **Powers M**, Liu J. Occupational chemical exposures among cosmetologists: risk of reproductive disorders. *Work Heal Saf*. 2013 Dec;61(12):522–528.

#### ORAL AND POSTER PRESENTATIONS

1. **Powers M**, Sanchez T, Grau-Perez M, Yeh F, Francesconi K, Goessler W, George CM, Heaney C, Best LG, Umans JG, Brown RH, Navas-Acien A. "Low-moderate Arsenic Exposure and Respiratory Health in American Indian Communities." Poster at International Society for Environmental Epidemiology (ISEE) on August 27, 2018. Ottawa, Canada.
2. **Powers M**, Sanchez T, Grau-Perez M, Yeh F, Francesconi K, Goessler W, George CM, Heaney C, Best LG, Umans JG, Brown RH, Navas-Acien A. "Low-moderate Arsenic Exposure and Respiratory Health in American Indian Communities." Poster at NIEHS Superfund Research Program Annual Meeting on December 7, 2017. Philadelphia, PA.
3. **Powers M**, Sanchez T, Yeh F, Navas-Acien A. "Low-moderate Arsenic Exposure and Respiratory Health in American Indian Communities: The Strong Heart Study."

- Oral presentation at Thomas L. Petty Aspen Lung Conference on June 8, 2017. Aspen, CO.
4. **Powers M**, Maruthur N, Howard B, Umans J, Lee E, Best LG, Navas-Acien A. "Association of Urine Zinc with Prevalent and Incident Diabetes in the Strong Heart Study." Oral presentation at International Society for Environmental Epidemiology (ISEE) on September 2, 2016. Rome, Italy.
  5. Saberi P, **Powers M**, McKenzie J. "Field Survey of Health Perception and Complaints of Pennsylvania Residents in Marcellus Shale Regions." Poster at American Public Health Association (APHA) Annual Meeting on November 6, 2013. Boston, MA.
  6. Saberi P, **Powers M**, McKenzie J. "Field Survey of Health Complaints of Pennsylvania Residents in Marcellus Shale Regions." Poster at 24<sup>th</sup> Annual Conference of the International Society for Environmental Epidemiology (ISEE) on August 27, 2012. Columbia, SC.
  7. **Powers, M**, Pepino, R. "Application of Superfund Law to Emerging Natural Resource Extraction in Pennsylvania." Oral presentation at American Water Works Association Annual Conference, PA Chapter, May 4, 2012. Lancaster, PA.
  8. **Powers M**, Gerber J. "Helping to Raise the Profile of Amherst Farms and the Importance of Purchasing Locally Grown Produce." Oral presentation at 13<sup>th</sup> Annual Statewide Undergraduate Research Conference, April 2007. Amherst, MA.